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STUDIES ON DISEASES OF MUSCLE

I. PROGRESSIVE MUSCULAR DYSTROPHY; A CLINICAL REVIEW OF FORTY CASES

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Progressive muscular dystrophy is characterized by degeneration and atrophy of striated muscle. The disease is heredofamilial. It is accompanied by an abnormality in creatine metabolism, with creatinuria in adults or by excessive urinary excretion of creatine in children. Within recent years the study of diseases of muscle has received new impetus from several sources. New information concerning the origin and metabolism of creatine, the discovery of a deficiency disease in animals which resembles progressive muscular dystrophy in man and new knowledge of the physiology of muscle and the chemistry of muscle contraction have made it advisable to reexamine the syndrome of progressive muscular dystrophy in the light of these advances. This paper presents a clinical description and the results of preliminary studies of 40 cases of this disease.

Original descriptions of the syndrome of progressive muscular dystrophy are credited to Meryon, 1852,[1] and to Duchenne, 1861.[2] Erb.[3] was the first to differentiate clearly between the muscular atrophies and the muscular dystrophies. In 1884 he described a spinal form of muscular atrophy, which he attributed to degeneration of the anterior horn cells, and a syndrome of muscular dystrophy, in which no such changes in the central nervous system were demonstrable.

Various clinical forms of muscular dystrophy have been described. Erb,[3] in 1884, reported on a juvenile type which differed from the syndrome described by Duchenne in that the onset occurred later in childhood and atrophy of the skeletal muscles was not accompanied by pseudohypertrophy. A facioscapulohumeral form which included involvement of the facial musculature, as well as the changes associated with the juvenile type of Erb, was described by Landouzy and Dejerine.[4] The earliest descriptions of muscular dystrophy characterized the disease as involving only the proximal muscles of the extremities, with sparing of the distal muscles of the hands, forearms and feet. However, Gowers,[5] in 1902, and Spiller,[6] in 1907, recognized a form of the disease with early changes in the distal musculature. Gowers,[7] in his monograph on pseudohypertrophic muscular paralysis, published in 1879, stated that "hypertrophy and atrophy may exist in different proportions and there are cases which connect the two extremes —in some enlargement of many muscles, and in others wasting of all." Erb[8] expressed the

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1. Meryon, E.: On Granular and Fatty Degeneration of the Voluntary Muscles, Med.-Chir. Tr., London **35**:73, 1852.

2. Duchenne, G. B. A.: Paraplégie hypertrophique congenitale: De l'électrisation localisée et son application à la pathologie et à la therapeutique, ed. 2, Paris, J.-B. Baillière et fils, 1861.

3. Erb, W.: Ueber die "juvenile Form" der progressiven Muskelatrophie und ihre Beziehungen zur sogenannten Pseudohypertrophie der Muskeln, Deutsches Arch. f. klin. Med. **34**:467 (March 27) 1884.

4. Landouzy, L., and Dejerine, J.: De la myopathie atrophique progressive (myopathie héréditaire débutant, dans l'enfance, par la face, sans altération du système nerveux), Compt. rend. Acad. d. sc. **98**:53 (Jan. 7) 1884.

5. Gowers, W. R.: A Lecture on Myopathy and a Distal Form, Brit. M. J. **2**:89 (July 12) 1902.

6. Spiller, W. G.: Myopathy of the Distal Type and Its Relation to the Neural Form of Muscular Atrophy (Charcot-Marie-Tooth Type), J. Nerv. & Ment. Dis. **34**:14, 1907.

7. Gowers, W. R.: Pseudohypertrophic Muscular Paralysis, London, J. & A. Churchill, 1879.

8. Erb, W.: Dystrophia muscularis progressiva, Deutsche Ztschr. f. Nervenh. **1**:173 (July 24) 1891.

opinion that all the clinical forms of muscular dystrophy were variations in manifestation of the same disease process. Such a view is still tenable, and clinical classifications of the disease are useful only in designating the muscle groups first affected and the age of onset of the disease.

The degenerative changes in progressive muscular dystrophy are extensive and are usually limited to skeletal muscle, although the myocardium may be involved.[9] Smooth muscle of the gastrointestinal tract and of other organs is believed to be unaffected. Pseudohypertrophy develops most commonly in large, bulky muscles, such as the soleus, gastrocnemius, gluteus, deltoid, supraspinatus and infraspinatus muscles and the muscles of the tongue. The increase in size of these muscles is due chiefly to an increase in the fat and connective tissue elements.

The muscles affected by dystrophy are pale. Microscopic changes are essentially the same in all forms of the disease. The fibrous connective tissue and the fat between the muscle bundles are increased in amount. Muscle fibers are decreased in diameter and in number and in many instances show longitudinal splitting. Accumulations of nuclei appear beneath the sarcolemmal sheaths. Within the fibers signs of degeneration are evidenced by vacuolation and by hyalinoid and granular changes. In late stages of the disease the muscle is almost completely replaced and only occasional muscle fibers may be seen.

DATA ON CASES

Forty patients comprised the series studied. All the patients had been seen previously in other clinics or by other physicians and referred to the Hospital of the Rockefeller Institute for Medical Research with the diagnosis of progressive muscular dystrophy. Patients for whom the diagnosis could not be confirmed were not included in this series. The criteria utilized in making the diagnosis of progressive muscular dystrophy were as follows: (*a*) a history of progressive muscular weakness and disability, (*b*) occurrence of other cases of the disease in the same family; (*c*) demonstrable atrophy or pseudohypertrophy of affected muscles, (*d*) hypoactivity or absence of tendon reflexes, (*e*) absence of signs referable to disease of the central nervous system and (*f*) creatinuria, in an adult, or increased excretion of creatine, in a child. Most of these patients have been followed clinically for from one to three years.

Sex Distribution.—Progressive muscular dystrophy has been shown to occur more frequently in males. In the series of cases reviewed by Gowers[7] there were 190 males and 30 females. Hough[10] reported a series of 28 cases in which there were no females. In the cases studied by Hurwitz,[11] 6 of 44 patients were females. Bell,[12] in a review of 1,324 cases reported in the literature, found that 73.1 per cent were males. Of the 40 patients included in the group described here, 35 were males and 5 females.

Age Distribution.—The youngest patient was 2½ and the oldest 57 years of age. The age distribution of the patients is shown in table 1.

TABLE 1.—*Age Distribution of Patients*

Age, Years.....	0-5	6-10	11-15	16-20	21-30	31-40	41-50	51-60
No. of patients....	5	14	2	3	4	9	1	2

It will be seen that 19 patients, or 47.5 per cent of the series, were less than 10 years of age.

Racial, National and Social Representation.—Muscular dystrophy occurs rarely in Negroes. Pearson[13] illustrated the case of a Negro boy, and Orbison[14] reported a case in a Negro woman. One Negro boy was included in the present series.

Most of the patients were inhabitants of the city of New York and were derived from family groups representing Russian, Italian, Hungarian, German, Irish, Lithuanian, Austrian and English nationalities. Thirteen of the 40 patients were of Jewish extraction. The percentage of patients derived from each of these national groups corresponded roughly with the distribution of these groups in the population of New York.

The patients represented all social levels. There was no evidence that the disease was more prevalent among the underprivileged. The histories indicated that the diets had been adequate, and unusual food habits were infrequent.

9. (*a*) Sachs, B., and Brooks, H.: Progressive Muscular Dystrophy, with the Report of an Autopsy, Am. J. M. Sc. **122**:54 (July) 1901. (*b*) Bunting, C. H.: Chronic Fibrous Myocarditis in Progressive Muscular Dystrophy, ibid. **135**:244 (Feb.) 1908. (*c*) Globus, J. H.: The Pathologic Findings in the Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:59 (Jan.) 1923. (*d*) Yoshida, T.: Ueber die Myokardveränderung bei der progressiven Muskeldystrophie, Jap. J. M. Sc., V, Path. **5**:63 (March) 1940.

10. Hough, G. de N., Jr.: Progressive Pseudohypertrophic Muscular Dystrophy: Report of the Results of Treatment with Adrenalin and Pilocarpin, with Analysis of Twenty-Eight Cases, J. Bone & Joint Surg. **13**:825 (Oct.) 1931.

11. Hurwitz, S.: Primary Myopathies: Report of Thirty-Six Cases and Review of the Literature, Arch. Neurol. & Psychiat. **36**:1294 (Dec.) 1936.

12. Bell, J.: On Pseudohypertrophic and Allied Types of Progressive Muscular Dystrophy, in Fischer, R. A.: The Treasury of Human Inheritance, London, Cambridge University Press, 1943, vol. 4, pt. 4.

13. Pearson, K.: Two New Pedigrees of Muscular Dystrophy, Ann. Eugenics **5**:179 (Jan.) 1933.

14. Orbison, T. J.: Myopathy, with Clinical Records of Eight Cases Comprising Various Types, Am. J. M. Sc. **148**:550 (Oct.) 1914.

Genetic Influences.—Meryon,[15] in 1866 and Gowers[7] in 1879, called attention to the factor of heredity in progressive muscular dystrophy. Bell[12] found genetic influences in 79 per cent of 1,341 cases recorded in the literature and reported that 47 of 114 cases in the National Hospital, Queens Square, London, occurred in families in which other cases had appeared. Genetic patterns have been found to be of various types, the disease following dominant, sex-linked or recessive factors. Weitz[16] noted that the dominant mode of transmission was accompanied by more frequent involvement of the muscles of the upper extremities, whereas the genetic patterns of muscular dystrophy with onset in childhood and involvement of the muscles of the calves and thighs were more likely to be recessive. Bell[17] found no evidence of earlier onset of the disease in later generations of families in which the disease occurred. Twenty-six of the 40 patients in our series were the only members with the disease in their respective families. However, many of the patients were unable to construct pedigrees including more than three generations. For 2 of the 14 patients from families in which other cases of progressive muscular dystrophy had occurred the disease was mediated through a dominant gene; for 5, through a sex-linked gene, and for 7, through a simple recessive gene.

Conditioning Factors in the Causation of the Disease.—It has been reported that the onset of progressive muscular dystrophy may follow infectious disease,[18] trauma[19] and overexertion.[19a] Only 5 of the 40 patients had a history of factors of this type. Two patients first showed signs of the disease after attacks of acute poliomyelitis. The mother of 1 patient had congenital syphilis. She had received antisyphilitic therapy in childhood, and the Wassermann reaction had been negative for many years prior to the birth of the child. The patient's Wassermann reaction was negative. Another patient had sustained an injury at birth. In 1 patient the first signs of the disease were noted after pregnancy.

Age of Onset.—The age of onset of the disease in this series of patients as determined by the time of appearance of the first symptoms is recorded in table 2. Twenty-five patients, or 62 per cent of the series, noted the first symptoms before the age of 10 years. In all of these patients the earliest signs of the disease were referable to changes in the muscles of the thighs and calves. Of the 15 patients whose muscular disabilities became apparent after the age of 10 years, 5 complained first of weakness of and noted atrophy in the scapulohumeral group of muscles.

TABLE 2.—*Age of Patients at Onset of Disease*

Age, Years	0-5	6-10	11-15	16-20	21-30	31-40	41-50
No. of patients	22	3	4	2	6	2	1

Clinical Course of the Disease.—In each of the 40 patients the dystrophic process appearing in one or more muscles progressed to involve other groups of muscles. The progress of the disease was most rapid in persons in whom the disease had its onset in infancy or early childhood. Of 22 patients in whom the first signs of the disease were noted before the age of 5 years, 8 were invalids and unable to walk by the age of 10 years, and the condition of 3 others had progressed to complete invalidism by the age of 15 years. Of the 15 patients in whom the disease had its onset after the age of 10 years, the condition of only 3 had progressed to complete invalidism twelve, sixteen and twenty-eight years, respectively, after the appearance of the first symptoms.

A complaint of cramping pains occurring early in the course of the disease in the affected muscles of the extremities and in the abdominal muscles was made by 14 patients. The pains were severe enough to keep the patients awake at night, and in the case of 1 patient the symptom led to a faulty diagnosis of acute appendicitis. There seemed to be no relation between prior use of the muscles and the onset of the pain. Spasm of the muscles at the site of the pain was observed in 1 patient, but the pain was usually unaccompanied by demonstrable muscular spasm. No mention of the occurrence of this symptom in cases of muscular dystrophy has been found in the medical literature, although pain was a frequent complaint in the present series.

15. Meryon, E.: On Granular Degeneration of the Voluntary Muscles, Med.-Chir. Tr., London **49**:45, 1866.

16. Weitz, W.: Ueber die Vererbung bei der Muskeldystrophie, Deutsche Ztschr. f. Nervenh. **72**:143 (Sept.) 1921.

17. Bell, J.: On the Age of Onset and Age at Death in Hereditary Muscular Dystrophy, with Some Observations Bearing on the Question of Antedating, Ann. Eugenics **11**:272 (May) 1942.

18. (*a*) Kaumheimer, L.: Progressive Muskeldystrophie nach (rezidivierender) Poliomyelitis, Ztschr. f. Kinderh. **25**:1 (May 8) 1920. (*b*) Gaupin, C. E.: Symposium on Muscular Dystrophies, Kentucky M. J. **23**:523 (Nov.) 1925. (*c*) Barnes, S.: A Myopathic Family, with Hypertrophic, Pseudohypertrophic, Atrophic and Terminal (Distal in Upper Extremities) Stages, Brain **55**:1 (March) 1932.

19. (*a*) Arbuse, D. I., and Sloane, D.: Muscular Dystrophy: Report of a Family, New York State J. Med. **37**:1111 (Jan. 15) 1937. (*b*) Gaupin.[18b] (*c*) Barnes.[18c]

All the patients had visited other clinics and had been treated by other physicians. Many types of therapy had been attempted, without improvement or arrest of the disease in any case. In table 3 are listed the therapeutic agents used and the number of patients receiving each form of treatment.

TABLE 3.—*Therapeutic Agents Used Prior to Beginning of This Study*

Type of Therapy	Number of Patients Treated
Amino acids	
Aminoacetic acid	14
Aminoacetic acid and ephedrine	5
Gelatin	3
Vitamins	
Thiamine	8
Riboflavin	4
Nicotinic acid	3
Pyridoxine	17
Ascorbic acid	2
Alpha tocopherol	17
Wheat germ oil	11
Glandular preparations	
Gonadotropin	3
Epinephrine and pilocarpine	3
Adrenal cortex extract	1
Androgen	1
Parathyroid extract	1
Miscellaneous agents	
Creatine	1
Potassium chloride	2
Amphetamine	2
Unsaturated fatty acids	2
Bile salts and bile salts and iron	1
Massage	10
Electrical stimulation	3
Hydrotherapy	5

PHYSICAL SIGNS

Physical examinations of the 40 patients in this series revealed various distributions of affected muscle groups and all stages in the course of the disease. Pseudohypertrophy was seen frequently in the younger patients and infrequently in the older ones. In many of the patients both pseudohypertrophy and atrophy existed in different groups of muscles. The muscles most commonly exhibiting pseudohypertrophy were the soleus, gastrocnemius, gluteus, deltoid, infraspinatus and supraspinatus muscles.

Involvement of muscles about the shoulder girdles produced characteristic winging of the scapulas. Lumbar lordosis was prominent when the muscles about the vertebral column and the extensors of the thighs were involved, a deformity that was pronounced in 21 patients. In 18 patients the atrophic process in the muscles of the calves produced shortening of the achilles tendon and talipes equinovarus. When muscles of the lower extremities were affected, there was a characteristic gait in which the feet were slapped down and the hips were shifted one ahead of the other to effect a forward motion.

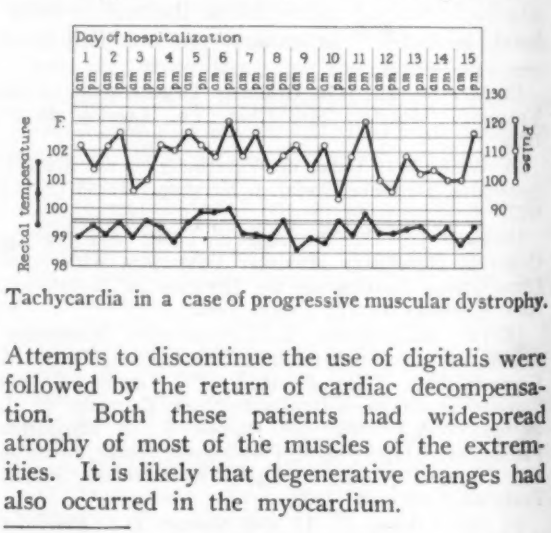
All the younger patients showed the sign of Gowers,[7] who described the movements necessary for persons with this disease to rise from a sitting position on the floor to a standing position. The patient turns over, supports himself on his hands and knees and, extending his legs at his knees, pushes himself gradually upward by placing his hands successively on his ankles, knees and hips.

Five of the 40 patients exhibited enlargement of the tongue. Each of these 5 patients also had involvement of the facial musculature, with a resultant transverse smile.

Fibrillary twitchings were not seen in the muscles of any of the patients. The superficial reflexes were normal. The tendon reflexes were hypoactive or absent, except that early in the involvement of the muscles of the calf the achilles tendon reflex was often hyperactive. There were no signs of an upper motor neuron defect.

Boas and Lowenburg[20] and Hurwitz[11] described pronounced tachycardia, with lability of the heart rate and excessive response to minimal stimuli in the patients whom they observed. The pulse rate during rest was characteristically high in the 40 patients of the present series. The pulse and temperature chart of 1 patient is reproduced in the figure.

Sachs and Brooks,[9a] Bunting[9b] and Globus[9c] reported on involvement of the myocardium by the dystrophic process. In 2 patients in the present series without previous signs or history of heart disease cardiac decompensation slowly developed, with dilatation of the heart. Roentgenograms showed a large, dilated heart, with limited movement of the ventricles in the roentgenokymogram. One of these patients had changes in the electrocardiogram suggestive of myocardial damage. Digitalization resulted in the disappearance of signs of decompensation.



Tachycardia in a case of progressive muscular dystrophy.

Attempts to discontinue the use of digitalis were followed by the return of cardiac decompensation. Both these patients had widespread atrophy of most of the muscles of the extremities. It is likely that degenerative changes had also occurred in the myocardium.

20. Boas, E. P., and Lowenburg, H.: The Heart Rate in Progressive Muscular Dystrophy, Arch. Int. Med. **47**:376 (March) 1931.

Gowers [7] described a reddish purple mottling of the skin which frequently accompanied progressive muscular dystrophy. This phenomenon was noted in all the younger patients and in many of the adults in our series. It was most pronounced in the skin over the lower half of the body.

The disease in its late stages frequently manifests lipodystrophy, large deposits of soft fat accumulating about the face, neck, hips and thighs. This change was conspicuous in 9 patients of the present series. Although all these patients had extensive muscular atrophy, the deposition of fat prevented the appearance of emaciation and aided in the maintenance of body contours.

Electrocardiographic Changes.—Electrocardiograms were taken at frequent intervals on all these patients. All of the records showed a rapid heart rate with normal or irregular sinus rhythm. No other electrocardiographic changes occurred with any frequency. In a patient who previously had shown left axis deviation right axis deviation developed, with lengthening of the Q-T interval, prior to the development of cardiac dilatation and decompensation. The results of a study of the electrocardiograms of these patients are to be reported in detail by Newman, Shank, Hoagland and Cohn.[21]

Roentgenograms.—Atrophy and malformations of bone have been described as part of the disease process in progressive muscular dystrophy by Wright [22]; Janney, Goodhart and Isaacson [23]; Hurwitz [11]; Maybarduk and Levine,[24] and Epstein and Abramson.[25] Roentgenograms were made of the skull, heart, lungs, vertebral column, pelvis, long bones, hands and feet of each of the 40 patients. There was streaking of the soft tissue shadows of affected muscles which was due to the contrasting mediums of muscle and of the infiltrating connective tissue and fat. The appearance of centers of ossification in the bones of the hands and in the epiphyses of the long bones was delayed. Evidences of demineralization were apparent in the bony structure of most of the patients. These changes were frequent and were considered characteristic of progressive muscular dystrophy. They will be described in detail in a later paper.

Other roentgenographic changes occurred less frequently and were considered incidental to the disease. Timme [26] reported early calcification of the pineal gland in cases of progressive muscular dystrophy. In our series 2 patients less than 20 years of age had calcification of the pineal body. One adult had a greatly enlarged sella turcica, with roentgenographic evidence of a pituitary adenoma. Two young adults had pronounced hyperostosis frontalis interna. There was roentgenographic evidence of pulmonary tuberculosis with cavitation in 1 patient and of pronounced cardiac hypertrophy in a patient with a history of rheumatic heart disease.

METABOLIC STUDIES

Twenty-two of the 40 patients were observed during periods of hospitalization in a metabolism ward. The rate of urinary excretion of creatine and creatinine, the fasting level of creatine and creatinine in the blood, the basal metabolic rate, the dextrose tolerance and the balance of nitrogen and of phosphorus were determined.

Rate of Urinary Excretion of Creatine and Creatinine.—The reports of numerous investigators have shown that changes in creatine and creatinine metabolism occur in progressive muscular dystrophy and that the increase in creatine output is to some extent proportional to the amount of affected musculature. Rosenthal,[27] in 1870, reported a decreased excretion of creatinine, an observation also made by Weiss,[28] in 1877, and by Langer,[29] in 1882. With the development of an improved method for the estimation of creatine and creatinine by Folin,[30] in 1904, more exact studies were made possible. Spriggs [31] con-

21. Newman, C.; Shank, R. E.; Hoagland, C. L., and Cohn, A. E.: The Electrocardiogram in Progressive Muscular Dystrophy, to be published.

22. Wright, C.: Consideration of Progressive Muscular Dystrophy with Pseudohypertrophy from an Endocrine Standpoint, California & West. Med. **23**: 999 (Aug.) 1925.

23. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

24. Maybarduk, P. K., and Levine, M.: Osseous Atrophy Associated with Progressive Muscular Dystrophy, Am. J. Dis. Child. **61**:565 (March) 1941.

25. Epstein, B. S., and Abramson, J. L.: Roentgenologic Changes in the Bones in Cases of Pseudohypertrophic Muscular Dystrophy, Arch. Neurol. & Psychiat. **46**:868 (Nov.) 1941.

26. Timme, W.: Progressive Muscular Dystrophy as an Endocrine Disease, Arch. Int. Med. **19**:79 (Jan.) 1917.

27. Rosenthal, M.: Handbuch der Diagnostik und Therapie der Nervenkrankheiten, Erlangen, F. Enke, 1870, p. 220.

28. Weiss, N.: Ueber einen Fall von progressiver Muskelatrophie, Wien. med. Wchnschr. **27**:701, 1877.

29. Langer, L.: Ein Fall von ausgebreiteter progressiver Muskelatrophie mit paralytischer Lendenlordose, Deutsches Arch. f. klin. Med. **32**:395 (Dec. 18) 1882.

30. Folin, O.: Beitrag zur Chemie des Kreatinins und Kreatins im Harne, Ztschr. f. physiol. Chem. **41**: 223 (March 5) 1904.

31. Spriggs, E. I.: The Excretion of Creatinin in a Case of Pseudo-Hypertrophic Muscular Dystrophy, Biochem. J. **2**:206, 1907.

firmed the earlier reports of decrease in urinary creatinine. Levene and Kristeller [32] first demonstrated that creatinuria usually accompanies the disease.

There were an increase in the creatine excretion and a decrease in the creatinine excretion of all the patients in this series. The rate of excretion of these substances was studied for 9 boys with muscular dystrophy between the ages of 6 and 11 years. This rate was compared with the rate of excretion for 5 normal boys of the same age group. The diets of all the subjects were similar and provided 3 Gm. of protein, 2 Gm. of fat and 6 Gm. of carbohydrate per kilogram of body weight per day. The foods containing precursors of creatine and creatinine were contained in constant and like amounts in all the diets. The amounts of creatine and creatinine in twenty-four hour specimens of urine were determined by a modification of Folin's [30] method, in which the photoelectric colorimeter was utilized. The results presented in table 4 include the average daily rates of excretion of creatine and creatinine

TABLE 4.—*Daily Excretion of Creatine and Creatinine in Normal Subjects and in Patients with Muscular Dystrophy*

Subject	Age, (Years)	Period of Study (Days)	Creatine as Creatinine, Average Daily Excretion (Mg. per Kilogram of Body Weight per Day)	Creatinine, Average Daily Excretion (Mg. per Kilogram of Body Weight per Day)
Normal Subjects				
J. B.	9	11	15.8	18.9
S. B.	11	9	9.7	19.6
R. D.	12	10	5.6	22.6
W. S	9	13	14.1	22.6
L. V.	11	11	9.2	24.2
Average			10.9	21.6
Patients with Muscular Dystrophy				
A. G.	8	13	18.8	13.1
R. G.	8	34	17.1	10.3
R. R.	5	32	16.7	18.7
D. W. S.	7	39	21.9	11.6
A. T.	11	17	23.0	9.5
G. T.	7	43	19.2	10.0
R. B.	6	15	20.0	14.0
D. S.	7	16	30.1	9.2
R. D. G.	11	15	33.7	13.7
Average			22.3	12.2

during the periods studied. The values for creatine represent creatine determined as creatinine.

Normal boys excreted from 5.6 to 15.8 mg. of creatine per kilogram of body weight per day on the diet indicated, an average of 10.9 mg per kilogram per day, while the boys with muscular dystrophy excreted daily from 16.7 to 33.7 mg. of creatine per kilogram of body weight, an average of 22.3 mg. per kilogram per day. Excretion of creatinine was greater for the normal boys, with an average daily urinary excretion of 21.6 mg. per kilogram and with rates of excretion varying from 18.9 to 24.2 mg. per kilogram. The average rate of excretion of creatinine for the patients with progressive muscular dystrophy was 12.2 mg. per kilogram per day, with extremes of 9.2 and 14 mg. per kilogram per day. Excretion of creatine for dystrophic patients was 204 per cent that of control children of the same sex and age group, whereas excretion of creatinine was only 56 per cent of the output of the control subjects.

TABLE 5.—*Fasting Plasma Concentrations and Urinary Excretion Rates of Creatine and Creatinine in Normal Subjects and in Patients with Muscular Dystrophy*

		Plasma Concentration		Urinary Excretion Rate	
Subject	Age (Years)	Creatine as Creatinine (Mg./100 Cc.)	Creatinine (Mg./100 Cc.)	Creatine as Creatinine (Mg. per Kilogram of Body Weight per Day)	Creatinine (Mg. per Kilogram of Body Weight per Day)
Normal Subjects					
L. V.	11	0.95	0.85	4.7	22.3
S. B.	11	0.74	0.86	3.7	22.3
W. S.	9	0.99	0.69	5.6	23.9
R. D.	12	1.06	0.70	4.3	13.1
J. B.	9	1.07	0.74	6.0	19.6
Average		0.96	0.77	5.0	19.7
Patients with Muscular Dystrophy					
A. T.	11	1.11	0.68	14.1	7.2
R. R.	7	1.17	0.67	15.5	6.9
D. W. S.	7	1.24	0.66	10.9	8.9
R. G.	8	1.24	0.67	14.1	7.4
A. G.	8	1.02	0.93	14.7	11.4
Average		1.16	0.72	13.8	8.3

When the subjects fasted for twenty-four hours to eliminate the effects of an intake of small amounts of precursors of creatine on creatine excretion, the differences were more pronounced. During the fasting period the rate of excretion of creatine and creatinine was determined for 5 boys with muscular dystrophy and for 5 normal boys. The fasting concentrations of creatine and creatinine in the plasma were also determined. The results are recorded in table 5.

In the fasting state, the average rate of excretion of creatine for the dystrophic patients was 282 per cent of the rate for the control subjects. The rate of excretion of creatinine was 42 per cent of that for the control group. The fasting concentration of creatine in the plasma was higher for the patients with muscular dystrophy, the average concentration being 1.16 mg. per hundred cubic centimeters, as compared with an

32. Levene, P. A., and Kristeller, L.: Factors Regulating the Creatinin Output in Man, Am. J. Physiol. **24**:45 (April) 1909.

average level of 0.96 mg. per hundred cubic centimeters for the normal subjects. Concentrations of creatinine in the plasma for these two groups were not significantly different. The average level for the dystrophic subjects was 0.72 mg. per hundred cubic centimeters and that for the normal group was 0.77 mg. per hundred cubic centimeters.

CREATINE TOLERANCE

It has been reported that the ability to retain ingested creatine is impaired in patients with progressive muscular dystrophy.[33] Milhorat and Wolff,[34] in a study of 17 dystrophic patients, observed retention of from 12 to 82 per cent of creatine ingested. The lowest retentions were in patients with extensive wasting of the muscles.

Tests for creatine tolerance were made on 5 boys with progressive dystrophy and on 4 normal boys. The subjects were placed for two days on diets which contained no meat, fish, fowl, coffee or tea. On the morning of the second day 1 Gm. of anhydrous creatine was given orally. The urinary output of creatine during the succeeding twenty-four hours was determined and compared with the output of the subjects on a similar diet to which no creatine had been added.

TABLE 6.—*Creatine Tolerance in Normal Subjects and in Patients with Muscular Dystrophy*

Subject	Creatine Retained, %
Normal Children	
J. B.	70.8
S. B.	58.6
R. D.	60.7
L. V.	83.5
Average	68.4
Children with Muscular Dystrophy	
A. T.	75.8
R. R.	63.5
D. W. S.	67.7
R. G.	45.4
J. S.	32.3
Average	56.9

In this manner the percentage of the ingested creatine retained was calculated. The results are shown in table 6.

The normal boys retained from 58.6 to 83.5 per cent of the creatine ingested, with an average retention for the group of 68.4 per cent. The greatest retention in the group of children with progressive muscular dystrophy was 75.8 per cent, while the least amount retained was 32.3 per cent. The average retention for this group was 56.9 per cent. All the patients had an advanced form of the disease, with pronounced and widespread muscular atrophy. However, it was not ascertained that the ability to retain ingested creatine was greatly impaired as compared with the creatine tolerance of normal children.

TABLE 7.—*Basal Metabolic Rates for Patients with Progressive Muscular Dystrophy*

Patient	Sex	Age, Years	Basal Metabolic Rate, %
E. L.	M	19	−14
A. T.	M	10	− 9
M. T.	M	8	−11
C. K.	F	9	−19
R. D. G.	M	11	−16
H. L.	M	51	−19
I. A.	M	35	−18
J. R.	M	9	−15
D. W. S.	M	6	− 4
A. G.	M	8	+ 1
J. S.	M	15	−24
L. G.	M	28	+10
R. A.	M	9	−13
E. M.	M	8	+ 1
Median			−14.5

BASAL METABOLIC RATE

It has been reported by Guarnaschelli-Raggio [35] and by Garot [36] that the basal metabolic rate is increased in patients with progressive muscular dystrophy. The basal metabolic rates were studied for 14 patients of this group. The results are given in table 7 and are expressed as percentages of the normal standards for age and sex according to Boothby and Sandiford.[37] The data represent the average for several determinations on each patient.

33. Gibson, R. B.; Martin, F. T., and Buell, M. V. R.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, Arch. Int. Med. **29**:82 (Jan.) 1922. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in the Myopathies, with Special Reference to Glycine Administration, J. A. M. A. **101**:1047 (Sept. 30) 1933. Milhorat, A. T.: Ueber die Behandlung der progressiven Muskeldystrophie und ähnlicher Muskelerkrankungen mit Glykokoll, Deutsches Arch. f. klin. Med. **174**:487 (Jan. 12) 1933. Levene and Kristeller.[32]

34. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992 (Nov.) 1937.

35. Guarnaschelli-Raggio, A.: La proteinemia nella distrofia muscolare progressiva primitiva, Arch. per lo stud. d. fisiopat. e clin. d. ricambio **6**:391 (Sept.-Oct.) 1938.

36. Garot, L.: Contribution à l'étude des troubles du métabolisme chimique dans la dénutrition grave du nourrisson: III. Excrétion créatinique et métabolisme basal, Rev. franç. de pédiat. **9**:273, 1933.

37. Boothby, W. M., and Sandiford, I.: Normal Values of Basal or Standard Metabolism: A Modification of the DuBois Standards, Am. J. Physiol. **90**: 290 (Nov.) 1929.

The median basal metabolic rate for the group of 14 patients was —14.5 per cent of the normal standards. Individual rates varied from —24 to +10 per cent. The results indicate that progressive muscular dystrophy is usually accompanied by a decrease in the basal metabolic rate.

INTRAVENOUS DEXTROSE TOLERANCE TEST

Abnormalities of carbohydrate metabolism in patients with progressive muscular dystrophy have been described by various investigators. McCrudden and Sargent,[38] Byard, [39] and Brock and Kay [40] observed low fasting levels of the blood sugar. McCrudden [41] expressed the opinion that the abnormality in dextrose metabolism is a causative factor in the malfunction of the diseased muscle. With oral dextrose tolerance tests, Janney, Goodhart and Isaacson [23] observed delayed utilization of dextrose. Hurwitz [11] and Magee,[42] however, reported an increased rate of utilization of dextrose when given by mouth. Scheman, Lewin and Soskin [43] and Elkington and Goldblatt [44] obtained normal responses to test doses of dextrose given orally.

Intravenous dextrose tolerance tests were performed on 9 patients with progressive muscular dystrophy and on 5 normal subjects. All of the subjects were made to fast for twelve hours prior to the administration of dextrose. Within ten minutes 0.5 Gm. of dextrose per kilogram of body weight was given intravenously as a 20 per cent solution in 0.9 per cent solution of sodium chloride. Fasting samples of blood were obtained, and samples were taken five, fifteen, thirty, forty-five, sixty, seventy-five and ninety minutes after completion of the venoclysis. The level of sugar in whole blood was determined by the method of Miller and Van Slyke.[45] Responses to intravenous injection of the dextrose solution are recorded in table 8.

In all the patients and the control subjects the sugar concentration of the blood had returned to fasting levels within seventy-five minutes of the administration of dextrose. In 1 subject there was evidence of rapid utilization of dextrose, the level of sugar in the blood dropping to 68 mg. per hundred cubic centimeters in thirty minutes and to 44 mg. per hundred cubic centimeters in ninety minutes. There were no clinicals signs of hypoglycemia in this or any other of the patients. The average fasting level of blood sugar was somewhat lower in the patients with muscular dystrophy, being 76.4 mg. per hundred cubic centimeters, as compared with an average fasting concentration of 85.4 mg. per hundred cubic centimeters for the 5 normal subjects. Average blood sugar levels at the various intervals following injection gave no indication of an increased or a decreased rate of utilization of dextrose in the dystrophic patients. With the single exception previously described, all dystrophic patients and control subjects gave responses to intravenous administration of dextrose within the normal limits for age and sex described by Crawford.[46]

NITROGEN AND PHOSPHORUS BALANCE

Meldolesi,[47] in a study of 48 cases of progressive muscular dystrophy, reported decreased urinary excretion of nitrogen, a delay in the secretion of lipase, diastase and trypsin in the intestine and low concentrations of these enzymes in the intestinal contents. From these observations, he concluded that the disease was the result of dysfunction of the pancreas, with the chief defect an inadequate absorption of protein and a depletion of protein reserves. Milhorat and Toscani,[48] who studied phosphorus, as well as calcium and magnesium, metabolism in 2 patients with progressive muscular dystrophy, were unable to demonstrate any signifi-

38. McCrudden, R. H., and Sargent, C. S.: Hypoglycemia and Progressive Muscular Distrophy, Arch. Int. Med. **17**:465 (April) 1916.

39. Byard, D. S.: Four Cases of Muscular Dystrophy, Internat. Clin. **1**:174, 1923.

40. Brock, S., and Kay, W. E.: A Study of Unusual Endocrine Disturbances: Their Associated Myopathies, Endocrine Balance and Metabolism Findings, Arch. Int. Med. **27**:1 (Jan.) 1921.

41. McCrudden, F. H.: The Nature of the Pathologic Process in Progressive Muscular Dystrophy, Arch. Int. Med. **21**:256 (Feb.) 1918.

42. Magee, M. C. M.: Creatine and Creatinine Metabolism in Progressive Muscular Dystrophy, Am. J. Dis. Child. **43**:19 (Jan.) 1932.

43. Scheman, L.; Lewin, P., and Soskin, S.: Pseudohypertrophic Muscular Dystrophy: An Evaluation of Recent Studies, J. A. M. A. **111**:2265 (Dec. 17) 1938.

44. Elkington, J. St. C., and Goldblatt, M. W.: Effect of Adrenaline in Certain Muscular Disorders, Lancet **2**:693 (Sept. 23) 1933.

45. Miller, B. F., and Van Slyke, D. D.: A Direct Microtitration Method for Blood Sugar, J. Biol. Chem. **114**:583 (July) 1936.

46. Crawford, T.: A Standard Intravenous Glucose Tolerance Test, Arch. Dis. Childhood **13**:69 (March) 1938.

47. Meldolesi, G.: Sulla terapia della distrofia muscolare progressiva a base di estratti pancreatici, Policlinico (sez. prat.) **43**:1187 (June 29) 1936.

48. Milhorat, A. T., and Toscani, V.: Studies in Diseases of Muscle: VIII. Metabolism of Calcium, Phosphorus and Magnesium in Progressive Muscular Dystrophy, Myotonia Atrophica and Familial Periodic Paralysis, Arch. Neurol. & Psychiat. **41**:1130 (June) 1939.

cant abnormality. Nevin[49] observed a low concentration of acid-soluble phosphorus in dystrophic muscles but stated that the changes demonstrated were secondary to degeneration of muscle and were not related to defects in mineral metabolism.

In a search for aberrations in nitrogen and phosphorus metabolism in patients with progressive muscular dystrophy, studies of nitrogen and phosphorus balance were made on 7 children with the disease. The patients were maintained on diets providing 3 Gm. of protein, 2 Gm. of fat and 6 Gm. of carbohydrate per kilogram of body weight per day. The urine and feces were collected for seven day periods.

TABLE 8.—*Results of the Intravenous Dextrose Tolerance Test for Normal Subjects and for Patients with Muscular Dystrophy*

Subject	Sex	Age, Years	Fasting	Blood Sugar Concentration, Mg./100 Cc. 5 Min.	15 Min.	30 Min.	45 Min.	60 Min.	75 Min.	90 Min.
Normal Subjects										
W. S.	M	9	88	231	189	154	128	105	90	74
S. B.	M	11	87	270	177	95	84	78	76	74
L. V.	M	11	89	241	194	147	115	96	92	87
J. B.	M	9	75	278	196	123	91	80	78	76
R. D.	M	12	88	235	194	154	133	98	89	80
Average			85.4	250.6	190	134	110.2	91.4	85	78.4
Patients with Muscular Dystrophy										
A. T.	M	11	78	199	179	119	98	80	72	70
G. T.	M	7	76	210	186	163	141	110	78	70
C. K.	F	9	84	281	217	185	165	107	100	95
I. A.	M	35	55	256	238	195	160	125	90	75
R. B.	M	6	73	195	132	68	60	71	71	44
D. W. S.	M	7	71	243	171	140	116	89	72	66
R. R.	M	5	88	251	256	182	128	104	90	85
R. G.	M	8	70	177	147	113	87	76	71	70
A. G.	M	8	95	207	173	136	124	108	93	77
Average			76.4	224.3	189	144.6	121	96.7	82.3	72.4

The macromethod of Kjeldahl[50] was used for the determination of nitrogen in the urine and the feces. The phosphorus content was determined by a modification of the method of Fiske and Subbarow.[51] The results are recorded in tables 9 and 10. The data given represent the average daily outputs and balances for the seven day periods.

Although the nitrogen content of the diets of these children was somewhat less than the usually accepted requirement for growing children,[52] the patients were maintained in positive nitrogen balance. The quantity of nitrogen retained was comparable to the amounts found by Porter[53] to be retained by normal children on a similar intake of protein. The loss of nitrogen in the feces was not excessive, and the urinary excretion of nitrogen was similar in quantity to that of normal children.[53] Therefore, no defect in the metabolism of nitrogen-containing compounds was apparent from these studies of the nitrogen balance. Retention of phosphorus was observed in all the patients studied. This indicates that no gross abnormality in phosphorus metabolism is associated with progressive muscular dystrophy, an observation which is in agreement with the earlier report of Milhorat and Toscani.[48]

COMMENT

A study of a primary degenerative disease of muscle, progressive muscular dystrophy, has been initiated at the Hospital of the Rockefeller Institute for Medical Research, with a series of 40 patients. The majority of the patients had onset of the disease in early childhood, with initial involvement of the muscles of the lower extremities. When the onset was delayed until late childhood or early adult life, the first muscles involved were frequently those of the scapulohumeral group. It was possible to demonstrate genetic influences for 14 of the 40 patients. There were examples of dominant, sex-linked and simple recessive types of inheritance. Both pseudohypertrophy and atrophy existed in affected muscles, with pseudohypertrophy most frequent in the large bulky muscles of the younger patients. The defects

49. Nevin, S.: A Study of the Muscle Chemistry in Myasthenia Gravis, Pseudohypertrophic Muscular Dystrophy and Myotonia, Brain **57**:239 (Oct.) 1934.

50. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: II. Methods, Baltimore, Williams & Wilkins Company, 1932, p. 516.

51. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375 (Dec.) 1925.

52. Holt, L. E., and Fales, H. L.: The Food Requirements of Children: II. Protein Requirement, Am. J. Dis. Child. **22**:371 (Oct.) 1921.

53. Porter, T.: Metabolism of Normal Pre-School Children: III. Variations in Nitrogen Storage on Constant Diets, J. Am. Dietet. A. **15**:427 (June-July) 1939.

produced by progressive muscular dystrophy in the patients of this series were similar to those described by other investigators. It was noted particularly that the original observations of Duchenne,[2] Erb,[3] Landouzy and Dejerine[4] and Gowers[7] were remarkably accurate and complete.

In all of the patients studied the disease was accompanied by increase in creatinuria (in children) or by the appearance of creatine in the urine (in adults). When the rates of excretion of creatine and creatinine for children with progressive muscular dystrophy were compared with the physiologic rates of excretion for normal children of the same age and sex, it was found that the excretion of creatine was notably increased and the excretion of creatinine was decreased. The amount of creatinine excreted daily by the patients in our series has remained remarkably constant during the months of study, whereas the quantity of creatine excreted has been much more variable.

The creatinuria of muscular dystrophy is modified by the administration of aminoacetic acid or the androgen testosterone. It was shown by Gibson and Martin[54] that excretion of creatine is increased by the feeding of gelatin. Brand and associates[55] obtained a similar and more profound effect from the administration of aminoacetic acid. Neither gelatin nor aminoacetic acid changed the rate of excretion of creatinine, however. Studies of the effect of testosterone propionate on the physiologic creatinuria of childhood and on the creatinuria of muscular dystrophy have been reported on by Hoagland, Shank and Gilder.[56] Evidence was obtained indicating that testosterone brings about retention and storage of creatine in patients with muscular dystrophy. Administration of testosterone produced no significant change in excretion of creatinine during the period studied.

TABLE 9.—*Nitrogen Balance in Patients with Muscular Dystrophy* *

Patient	Sex	Age, Years	Weight, Kg.	Nitrogen Intake, Gm.	Feces Nitrogen, Gm.	Urine Nitrogen, Gm.	Total Nitrogen Output, Gm.	Nitrogen Balance, Gm.
D. S.	M	7	25.5	8.00	0.736	6.491	7.227	+0.773
				8.00	0.794	6.072	6.866	+1.134
				8.00	0.742	6.227	6.969	+1.031
				8.00	0.731	6.369	7.100	+0.900
				8.00	0.729	6.074	6.803	+1.197
C. K.	F	9	36.2	11.29	0.513	9.766	10.279	+1.011
				11.29	0.962	9.474	10.436	+0.854
				11.29	0.952	9.007	9.959	+1.331
				11.29	0.926	11.290	12.216	−0.926
				11.29	0.866	9.603	10.469	+0.821
J. R.	M	9	34.0	8.00	0.717	5.748	6.465	+1.535
				8.00	0.693	5.559	6.252	+1.748
				8.00	0.508	6.229	6.737	+1.263
				8.00	0.677	5.871	6.548	+1.452
				8.00	0.602	5.925	6.527	+1.473
G. T.	M	6	24.2	8.00	0.606	6.438	7.044	+0.956
				8.00	0.718	5.936	6.654	+1.346
				8.00	0.607	5.891	6.498	+1.502
				8.00	0.553	6.818	7.371	+0.629
				8.00	0.712	5.902	6.614	+1.386
R. R.	M	4	21.3	10.25	0.764	9.290	10.054	+0.200
				10.24	0.668	8.995	9.663	+0.577
				10.23	0.596	9.474	10.070	+0.161
				9.74	0.615	9.939	10.545	−0.805
				10.25	0.718	9.760	10.478	−0.225
D. W. S.	M	6	21.0	10.21	0.666	9.484	10.150	+0.060
				10.26	0.867	9.046	9.913	+0.345
				10.25	0.621	9.335	9.956	+0.294
				10.25	0.924	9.270	10.194	+0.056
				10.25	0.735	8.383	9.118	+1.132
R. G.	M	8	27.5	13.43	0.966	11.497	12.463	+0.967
				13.44	0.506	9.811	10.317	+3.123
				13.44	1.154	10.425	11.579	+1.861
				13.46	1.146	11.546	12.546	+0.911
				13.44	1.777	11.087	12.864	+0.576

* All data given are in terms of grams per day and represent the average intake or output of nitrogen for each balance study period of seven days.

The metabolic changes that accompany progressive muscular dystrophy are not limited to the changes in excretion of creatine and creatinine. Evidence has been presented to show that the basal metabolic rate is decreased. In late stages of the disease there are increased

54. Gibson, R. B., and Martin, F. T.: Some Observations on Creatine Formation in a Case of Progressive Pseudohypertrophic Muscular Dystrophy, J. Biol. Chem. **49**:319 (Dec.) 1921.

55. Brand, E.; Harris, M. M.; Sandberg, M., and Ringer, A. I.: Studies on the Origin of Creatine, Am. J. Physiol. **90**:296 (Oct.) 1929.

56. Hoagland, C. L.; Shank, R. E., and Gilder, H.: Effect of Testosterone Propionate and Methyl Testosterone on Creatinuria in Progressive Muscular Dystrophy; Proc. Soc. Exper. Biol. & Med. **55**:49 (Jan.) 1944.

deposits of subcutaneous fat and infiltration of muscle by fat and connective tissue. In roentgenograms of patients with the disease there are evidences of abnormality in the calcifying process of bone, as shown by the frequent occurrence of delayed ossification of the bones of the hands and the epiphyses of the long bones and by demineralization of other bony structures. There is, however, no evidence of abnormality in dextose tolerance or in nitrogen or phosphorus balance. Undoubtedly, specific metabolic changes occur in the affected musculature, but these have not as yet been discovered or clarified. Investigations concerned with various processes and stages of intermediary muscle metabolism in progressive muscular dystrophy are under way in this laboratory and will be reported on subsequently.

Within recent years various types of therapy, including treatment with aminoacetic acid,[57] vitamin E[58] and pyridoxine,[59] have been proposed for progressive muscular dystrophy. Each of these methods has, after thorough trial, proved singularly ineffective. Any rational approach to the successful treatment of the disease depends on more specific information concerning its nature and the metabolic changes effected by it.

TABLE 10.—*Phosphorus Balance in Patients with Muscular Dystrophy* *

Patient	Sex	Age, Years	Weight, Kg.	Phosphorus Intake, Gm.	Feces Phosphorus, Gm.	Urine Phosphorus, Gm.	Total Phosphorus Output, Gm.	Phosphorus Balance, Gm.
D. S.	M	7	25.5	0.920	0.329	0.549	0.878	+0.042
				0.935	0.329	0.489	0.818	+0.117
				0.935	0.284	0.557	0.841	+0.094
				0.935	0.293	0.574	0.867	+0.068
				0.935	0.283	0.466	0.749	+0.168
C. K.	F	9	36.2	1.023	0.329	0.595	0.924	+0.099
				1.023	0.460	0.591	1.051	−0.028
				0.999	0.220	0.625	0.845	+0.154
				1.010	0.321	0.746	1.067	−0.057
				1.033	0.315	0.655	0.970	+0.063
J. R.	M	9	34.0	0.941	0.322	0.388	0.710	+0.231
				0.941	0.276	0.504	0.780	+0.161
				0.948	0.335	0.509	0.844	+0.104
				0.942	0.321	0.509	0.830	+0.112
				0.941	0.256	0.518	0.774	+0.167
G. T.	M	6	24.2	0.941	0.268	0.564	0.832	+0.109
				0.941	0.361	0.401	0.762	+0.179
				0.941	0.274	0.509	0.783	+0.158
				0.928	0.202	0.562	0.764	+0.164
				0.928	0.301	0.452	0.753	+0.175
R. R.	M	4	21.3	1.296	0.531	0.810	1.341	−0.045
				1.280	0.453	0.727	1.180	+0.100
				1.293	0.449	0.675	1.124	+0.169
				1.228	0.500	0.759	1.259	−0.031
				1.306	0.531	0.742	1.273	+0.033
D. W. S.	M	6	21.0	1.280	0.502	0.656	1.158	+0.122
				1.257	0.488	0.651	1.139	+0.118
				1.278	0.539	0.613	1.152	+0.126
				1.278	0.595	0.629	1.224	+0.054
				1.268	0.529	0.685	1.214	+0.054
R. G.	M	8	27.5	1.518	0.588	0.719	1.307	+0.274
				1.609	0.894	0.642	1.536	+0.073
				1.608	0.802	0.599	1.402	+0.206
				1.609	0.845	0.715	1.570	+0.039
				1.662	0.888	0.688	1.576	+0.086

* All data given are in terms of grams per day and represent the average intake or output of phosphorus for each balance study period of seven days.

SUMMARY

A clinical study of 40 patients with progressive muscular dystrophy gave evidence of the

57. Braestrup, P. W.: The Action of Glycine (Glycocoll) on Muscular Dystrophy and Other Diseases, Acta med. Scandinav. **89**:231, 1936. Mettel, H. B.: Pseudohypertrophic Muscular Dystrophy: Further Observations of the Therapeutic Effects of Glycine and Other Substances Used in the Treatment of Fourteen Cases of Muscular Dystrophy, J. Pediat. **5**:359 (Sept.) 1934.

58. (*a*) Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, Am. J. M. Sc. **202**: 258 (Aug.) 1941. (*b*) Viets, H. R.; Trowbridge, E. H., and Gunderson, T. E.: The Treatment of Certain Muscular Atrophies with Vitamin E, with a Note on Diagnosis and the Electromyograms, ibid. **203**:558 (April) 1942. (*c*) McBryde, A., and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy, J. Pediat. **18**:727 (June) 1941. (*d*) Lubin, A. J.: Use of Alpha Tocopherol in the Treatment of Neuromuscular Disorders, Arch. Int. Med. **69**:836 (May) 1942. (*e*) Hawke, W. A.: Vitamin Therapy of Muscular Dystrophy, Canad. M. A. J. **47**:153 (Aug.) 1942. (*f*) Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B_6: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, J. A. M. A. **116**:1895 (April 26) 1941.

59. McBryde and Baker.[58c] Hawke.[58e] Ferrebee and associates.[58f]

hereditary nature of the disease. Fourteen of the 40 patients were from families in which other cases of the disease had occurred.

The early onset of the disease was demonstrated, the first symptoms having been noted by 62 per cent of this series of patients before the age of 10 years.

The course of progressive muscular dystrophy was most rapid in patients with onset of the disease before the fifth year of life.

There were characteristic changes in the roentgenograms of patients with progressive muscular dystrophy. These alterations include conspicuous streaking of the soft tissue shadows of affected muscle, delayed appearance of centers of ossification in the bones of the hands and in the epiphyses of the long bones and demineralization of other bony structures.

The rate of excretion of creatine was greater and the rate of excretion of creatinine was less in boys with muscular dystrophy than in normal boys of the same age group who were maintained on diets of identical composition. These differences were increased when the subjects were fasting.

The concentration of creatine in the plasma of dystrophic children was greater than the concentration in the plasma of normal subjects. Levels of creatinine in the plasma were unchanged.

The creatine tolerance of children with progressive muscular dystrophy was not significantly different from that of normal children of the same age group.

The basal metabolic rate was low in children with the disease. The median basal metabolic rate for a group of 14 patients was —14.5 per cent of normal standards.

The fasting level of the blood sugar and the response to intravenous administration of dextrose were essentially the same in dystrophic patients as in normal subjects. One patient with muscular dystrophy gave evidence of an increased rate of utilization of dextrose injected intravenously.

Patients with progressive muscular dystrophy were in positive nitrogen and phosphorus balance.

PATHOLOGY OF DEMYELINATING DISEASES AS AN ALLERGIC REACTION OF THE BRAIN

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An important controversial issue is the interpretation of the pathology of primary demyelinating processes of the central nervous system. Neuropathologists have had considerable difficulty in agreeing on the significance of the vascular and perivascular reactions often observed with demyelinating diseases of the central nervous system. One group of investigators speaks of such conditions as degenerative and another as inflammatory. A conciliatory attitude is taken by workers who claim that the perivascular reaction is the expression of so-called symptomatic inflammation, a local reaction to disintegrated material. This controversy has run its gamut in the evaluation and interpretation of multiple sclerosis, diffuse sclerosis and the demyelinating encephalomyelitides following vaccination and infectious diseases, such as measles, scarlet fever, influenza and rabies.

PATHOGENESIS

Multiple Sclerosis.—One needs only cite Hassin's[1] opinion that this disease is degenerative and that the perivascular reaction is formed mainly, if not exclusively, of gitter cells. Lymphocytes, according to this author, may be present, but in very small numbers, and in the majority of cases are absent altogether. The lymphocytes when present denote a reaction against invasion of foreign substances from the parenchyma, such as gitter cells. Hassin stated the opinion that there would be no grounds for designating multiple sclerosis as an inflammatory process because of the occasional presence of a few lymphocytes and for ignoring the immense phenomena of degeneration.

Conversely, Steiner[2] was positive in the statement that multiple sclerosis is an inflammatory disease and that perivascular infiltration of lymphocytes and plasma cells is a common feature, especially in the acute stage or in the stage of reactivation of a chronic process. In cases of a protracted course a mixture of lymphocytes and compound granular corpuscles surrounds the blood vessels.

"Diffuse Sclerosis."—One may conclude from Bouman's[3] monograph that the pathologic process in this disease, like that of multiple sclerosis, is regarded as degenerative by one group of authors and as inflammatory by another. Marie and Foix,[4] Kraus and Weil,[5] Hermel,[6] Bouman[3] (case 1), Globus and Strauss[7] and Davison and Schick[8] stated that in sporadic cases the process is degenerative. In cases of the familial form, such as those described by Scholz,[9] the pathologic process was asserted to be essentially degenerative. Conversely, Schilder,[10] Bielschowsky and Henneberg,[11] Kufs,[12] Neubürger,[13] Siemerling and

From the Department of Neuropathology, New York State Psychiatric Institute and Hospital.

1. Hassin, G.: Histopathology of the Peripheral and Central Nervous System, New York, Paul B. Hoeber, Inc., 1940.

2. Steiner, G.: Multiple und diffuse Sklerose, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 289.

3. Bouman, L.: Diffuse Sclerosis, Bristol, England, John Wright & Sons, Ltd., 1934.

4. Marie, P., and Foix, C.: Sclérose intracérébrale et symmetrique, Rev. neurol. **27**:1, 1914.

5. Kraus, W. M., and Weil, A.: An Unusual and Protracted Case of Schilder's Disease, J. Nerv. & Ment. Dis. **62**:620, 1925.

6. Hermel, H.: Ueber einen Fall von Encephalo-Myelomalacia chronica diffusa, Deutsche Ztschr. f. Nervenh. **68**:338, 1921.

7. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy, Arch. Neurol & Psychiat. **20**:1190 (Dec.) 1928.

8. Davison, C., and Schick, W.: Encephalopathia Periaxialis Diffusa, Arch. Neurol. & Psychiat. **25**:1063 (May) 1931.

9. Scholz, W.: Klinische pathologisch-anatomische und erbbiologische Untersuchungen bei familiärer diffuser Hirnsklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:651, 1925.

10. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sclerose (Ueber Encephalitis periaxialis diffusa), Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912.

11. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffuse Sklerose (Leukodystrophia cerebri progressiva hereditaria), J. f. Psychol. u. Neurol. **33**: 12, 1927.

12. Kufs, H.: Ein bemerkenswerter Uebergangsfall von diffusen zu multiplen Hirnsklerose, Arch. f. Psychiat. **93**:564, 1931.

13. Neubürger, K.: Histologisches zur Frage der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:336, 1921.

Creutzfeld [14] and Jakob [15] concluded that the process was inflammatory, basing their conclusion partly on the presence of a perivascular infiltration of hematogenous elements and partly on the presence of the triad of degeneration, proliferation and exudation. Other authors, such as Weimann,[16] Anton and Wohlwill,[17] Walter [18] and Guttmann,[19] stated that the perivascular infiltration, if not pronounced, was an expression of a secondary reaction to the breakdown of the nerve parenchyma: "symptomatic inflammation."

In the presence of such opposing opinions, Bouman [3] concluded that the nature of the pathologic process in diffuse sclerosis, whether inflammatory or degenerative, is as yet undecided. It is disconcerting that in the two important conditions with patchy and diffuse demyelination neuropathologists of experience are unable to agree on the interpretation of the histopathologic process.

Demyelinating Encephalomyelitides.—A similar controversy exists concerning the interpretation of the histopathologic changes in the acute encephalomyelitides following vaccination or infectious diseases, such as measles, chickenpox, scarlet fever and influenza. Here also, while one group of investigators is convinced of the typical inflammatory nature of the pathologic process, another is hesitant in the definition and speaks of an encephalopathy or of an inflammatory process with special characteristics.

The controversy has also extended into the field of so-called acute multiple sclerosis. Of course, for investigators who deny the inflammatory nature of the pathologic process of multiple sclerosis there is no room for an acute inflammatory stage of that disease, whereas the acceptance of an acute inflammatory process in the acute phase of the disease becomes easier for those who believe in the inflammatory nature of multiple sclerosis and regard the full blown disease as its chronic stage. The same variations of opinion are encountered in the literature concerned with the interpretation of so-called Devic's disease, or acute optic neuroencephalomyelopathy. Although many authors have stated that this condition is a clinicopathologic entity, others have claimed that it is an acute encephalomyelitis, akin to acute multiple sclerosis. Marinesco, Draganesco, Sager and Grigoresco [20] stated that there are transitory stages between ophthalmoneuromyelitis and diffuse sclerosis. Here, also, one finds conflicting reports and interpretations as to the nature of the histopathologic process. To mention the reports of only a few authors, while in Beck's [21] cases lymphocytic and leukocytic infiltration was dominant, in the case of Guillain, Alajouanine, Bertrand and Garcin [22] the process was concluded to be degenerative.

The question has been raised why in the presence of different etiologic agents the cerebral pathologic changes in the encephalitides following various infectious diseases are fundamentally the same. How can one reconcile the fact that after vaccination against smallpox or rabies pathologic changes in the brain are identical with those following measles, scarlet fever or chickenpox, in which different viruses, or even a streptococcus, may be at work? Yet Bassoe and Grinker [23] asserted that the cerebral changes of encephalomyelitis due to rabies vaccine were identical with the changes following the use of cowpox vaccine or an attack of smallpox or measles. In their case of encephalomyelitis following subcutaneous injection of fourteen doses of 2 cc. of the rabies (Pasteur) vaccine, the changes were striking in the spinal cord, where lymphocytes and gitter cells were observed about the blood vessels in areas corresponding chiefly to the patches of demyelination. Since the encephalomyelitis following use of rabies vaccine and cowpox vaccine resembles nonvaccinal encephalomyelitis associated with smallpox, measles and other virus diseases, it is likely, they concluded, "that we are dealing with an inflammatory disease caused by an attenuated virus."

14. Siemerling, E., and Creutzfeld, H.: Bronzekrankheit und sklerosierende Encephalomyelitis, Arch. f. Psychiat. **68**:217, 1923.

15. Jakob, A.: Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihren Beziehungen zur diffusen und multiplen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **27**:290, 1915.

16. Weimann, W.: Zur Kenntnis der sogennanten diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **104**:411, 1926.

17. Anton, G., and Wohlwill, F.: Multiple nichteitrige Encephalomyelitis und multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:31, 1912.

18. Walter, F. K.: Zur Symptomatologie und Anatomie der diffusen Hirnsklerose, Monatschr. f. Psychiat. u. Neurol. **94**:87, 1918.

19. Guttmann, E.: Zur Kasuistik der "sklerosierenden Encephalitis," Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:62, 1925.

20. Marinesco, G.; Draganesco, S.; Sager, O., and Grigoresco, D.: Sur une forme particulière anatomo-clinique d'opthalmo-neuromyélite, Rev. neurol. **2**:193, 1930.

21. Beck, G.: A Case of Diffuse Myelitis Associated with Optic Neuritis, Brain **50**:687, 1927.

22. Guillain, G.; Alajouanine, T.; Bertrand, I., and Garcin, R.: Sur une forme anatomo-clinique spéciale de neuromyélite optique necrotique aïgue, Ann. de méd. **24**:24, 1928.

23. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis, Arch. Neurol. & Psychiat. **23**:1138 (June) 1930.

The possibility that encephalitis following vaccination results from an activated virus has been considered, and recently Milligan and Neubürger,[24] reporting on the pathologic changes of postvaccinal encephalitis in adults, emphasized the negative aspect of their bacteriologic investigation.

This difficulty in reconciling the similarity of the pathologic process with the action of various etiopathogenic agents is reflected in the perplexity expressed by Winkelman,[25] when, in order to explain the pathologic features of cerebral complications following scarlet fever, he resorted to the hypothesis that the streptococcus releases a virus dormant in the central nervous system, and added that "unless the same virus is released in the other acute exanthematic infectious processes . . . it is impossible to correlate the whole group."

From this brief review one can conclude that confusion exists not only in the evaluation of the pathologic process of multiple and of diffuse sclerosis, the cause of which is still a baffling problem, but in the interpretation of identical changes in the central nervous system developing in the course of diseases the etiologic factor of which is better known.

Interest and speculation have been stimulated concerning the possibility that there is, as the basis of these various processes, a common factor, a common denominator, the action of which may result in similarities in the pathologic reactions of the brain.

A detailed study of histopathologic data obtained from my own material and from material reported in the literature has gradually led me to believe that a common ground for evaluation of the pathologic changes of the central nervous system in this large and apparently varied group of diseases could be found by viewing the histologic picture as an allergic reaction.

Clinically it is suggested in the literature that some of the acute encephalomyelitides may be considered as allergic manifestations. This clinical attempt to regard allergy as the etiologic factor in demyelinating diseases has extended to both the chronic and the acute demyelinating processes. Glanzmann [26] gave various arguments in favor of the interpretation of the nervous complications of chickenpox, smallpox and vaccination as anaphylactic reactions. Van Bogaert [27] asserted that the nervous sequelae of vaccination were the expression of a hyperallergic reaction of the nervous system resulting from insufficiency of the "cutaneous pexic functions" (Dujardin). Finley,[28] in a discussion of the pathogenesis of encephalitis occurring with vaccination, smallpox and measles, offered clinical evidence that the response of the brain, like that of other tissues or organs of the body, is allergic and that the period of incubation of the encephalitis corresponds to the period of the particular exanthem with which it occurs. He stated that as yet little is understood of the reactions of hypersensitivity and immunity in the brain. Kennedy [29] stated that the clinical events of multiple sclerosis resemble the events of localized allergic edema of the central nervous system. Reese [30] also advocated study of these diseases from the standpoint of allergy. Pardee,[31] Rowe [32] and Winkelman and Moore [33] reported clinical cases of nervous manifestations which they related to allergic reaction of the nervous system; Marburg,[34] in referring to the Shwartzman phenomenon of local tissue reactivity, expressed the opinion that a similar mechanism may exist in multiple sclerosis.

The same uncertainties existing in the clinical and pathologic interpretation of demyelinating disease are encountered with respect to their causation, as is evident from a brief review of the etiologic theories advanced.

ETIOLOGIC THEORIES

Infectious Origin.—For multiple sclerosis and diffuse sclerosis, the theory of an infectious

24. Milligan, R. M., and Neubürger, K.: Post-Vaccinal Encephalitis in Adults, J. Neuropath. & Exper. Neurol. **1**:416, 1942.

25. Winkelman, N. W.: Scarlatinal Encephalomyelitis, J. Neuropath. & Exper. Neurol. **1**:363, 1942.

26. Glanzmann, E.: Die nervösen Komplikationen der Varizellen, Variola und Vakzine, Schweiz. med. Wchnschr. **57**:145, 1927.

27. van Bogaert, L.: Essai d'interpretation des manifestations nerveuses observées au cours de la vaccination de la maladie sérique et des maladies éruptives, Rev. neurol. **2**:1, 1932.

28. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047 (May) 1938.

29. Kennedy, F.: Allergy and Its Effects on the Central Nervous System, J. Nerv. & Ment. Dis. **88**: 91, 1938.

30. Reese, H. H.: Multiple Sclerosis, in Reese, H. H.; Lewis, N. D. C., and Sevringhaus, E. L.: The Year Book of Neurology, Psychiatry and Endocrinology, Chicago, The Year Book Publishers, Inc., 1942, p. 180.

31. Pardee, I.: Allergic Reactions in the Central Nervous System: Report of Two Cases, Arch. Neurol. & Psychiat. **39**:1360 (June) 1938.

32. Rowe, A. H.: Clinical Allergy in the Nervous System, J. Nerv. & Ment. Dis. **99**:854, 1944.

33. Winkelman, N. W., and Moore, M. T.: Allergy and Nervous Diseases, J. Nerv. & Ment. Dis. **93**:736, 1941.

34. Marburg, O.: New Studies in Multiple Sclerosis: Paraencephalomyelitis Periaxialis Scleroticans, J. Mt. Sinai Hosp. **9**:640, 1942.

origin, based on Chevassut's work and supported by the investigations of Purves-Stewart [35] (Spherula insularis), is discredited, as is the theory of the spirochetal origin of the process (Spirochaeta argentinensis), as advocated by Kuhn and Steiner.[36]

Toxic Origin.—The toxic origin of the disease (toxemia in the general sense) was advocated by Hallervorden and Spatz.[37] More specifically, lead (Cone, Russel and Harwood [38]), arsenic (Ecker and Kernohan [39]) and carbon monoxide (Hilpert [40]) have been mentioned as causation factors. Experimentally, tetanus toxin (Claude [41]; Putnam, McKenna and Evans [42]), saponin, sodium taurocholate, streptolysin (Weil [43]), carbon monoxide (Putnam and associates [44]), potassium cyanide (Ferraro [45], Rubino,[46] Hurst [47]), vinilamin (Luzzatto and Levi [48]), sulfanilamide (Fisher [49]) and cultures of Aspergillus fumigatus (Ceni and Besta [50]) have been considered as etiologic agents.

Lipolytic Theory.—Studies of lipolytic origin, initiated by Marburg,[51] have been followed, with variations, by Quinan,[52] Brickner,[53] Crandall and Cherry,[54] Altmann and Goldhammer [55] and Weil and Cleveland.[56] The presence of myelinolytic substance has been reported by Weil and Luhan [57] in the urine of patients with disseminated sclerosis.

Theory of Vascular Obstruction.—This theory has been developed to a considerable extent by Putnam [58] and his co-workers McKenna, Morrison and Alexander,[59] who predicated the occurrence of vascular thrombi as the cause of the parenchymatous changes. Experimentally, Putnam [60] and co-workers (Hoefer and Gray [61]) were able to reproduce encephalitis and sclerotic plaques with intravenous injections of oil or various coagulants.

Allergic Theory.—This theory, which has been mentioned clinically by various authors, but never interpreted satisfactorily from the pathologic standpoint, seems to have developed from various sources. Reports already exist in

35. Purves-Stewart, J.: Disseminated Sclerosis: Experimental Vaccine Treatment, Lancet **1**:440, 1930.

36. Kuhn, P., and Steiner, G.: Ueber die Ursache der multiplen Sklerose, Ztschr. f. Hyg. u. Infektionskr. **90**:417, 1920.

37. Hallervorden, T., and Spatz, H.: Ueber die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprocessen, Arch. f. Psychiat. **98**:641, 1935.

38. Cone, W.; Russel, C., and Harwood, R. U.: Lead as a Possible Cause of Multiple Sclerosis, Arch. Neurol. & Psychiat. **31**:236 (Feb.) 1934.

39. Ecker, A. D., and Kernohan, J. W.: Arsenic as a Possible Cause of Subacute Encephalomyelitis, Arch. Neurol. & Psychiat. **45**:24 (Jan.) 1941.

40. Hilpert, P.: Kohlenoxydvergiftung und multiple Sklerose, Arch. f. Psychiat. **89**:117, 1929.

41. Claude, H.: Myelite éxperimentale sub-aiguë par intoxication tetanique, J. de physiol. et de path. gén. **29**:843, 1897.

42. Putnam, T. J.; McKenna, T. B., and Evans, J.: Experimental Multiple Sclerosis in Dogs from Injection of Tetanus Toxin, J. f. Psychol. u. Neurol. **44**: 460, 1932.

43. Weil, A.: The Effect of Hemolytic Toxins on Nervous Tissue, Arch. Path. **9**:828 (April) 1930.

44. Putnam, T.; Morrison, L., and McKenna, J.: Experimental Demyelination, Tr. Am. Neurol. A. **57**: 451, 1931.

45. Ferraro, A.: Experimental Toxic Encephalomyelopathy, Psychiatric Quart. **7**:267, 1933.

46. Rubino, A.: Alterazioni della mielina da tossici, Riv. di pat. nerv. **45**:191, 1935.

47. Hurst, W.: Experimental Demyelination of the Central Nervous System, Australian J. Exper. Biol. & M. Sc. **120**:297, 1942.

48. Luzzatto, R., and Levi, A.: L'action de la vinilamin sur le système nerveux, Arch. internat. de pharmacodyn. et de therap. **26**:5, 1922.

49. Fisher, J. H.: Encephalomyelitis Following Administration of Sulphanilamide, Lancet **2**:301, 1939.

50. Ceni, C., and Besta, C.: Sclerosi in placche sperimentale da tossici aspergillari, Riv. sper. di freniat. **31**:125, 1905.

51. Marburg, O.: Die sogennante akute multiple Sklerose, Jahrb. f. Psychiat. **27**:211, 1906.

52. Quinan, C.: On Regional Lipolytic Activity in the Normal Human Brain, J. M. Research **35**:79, 1916.

53. Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**: 715 (April) 1930; Recent Experimental Work on the Pathogenesis of Multiple Sclerosis, J. A. M. A. **106**: 2117 (June 20) 1936.

54. Crandall, L. A., Jr., and Cherry, I. S.: Blood Lipase, Diastase and Esterase in Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:367 (Feb.) 1932.

55. Altmann, O., and Goldhammer, H.: Lipase und Cholesterinbestimmungen bei der multiplen Sklerose, Klin. Wchnschr. **2**:1017, 1937.

56. Weil, A., and Cleveland, D. A.: A Serologic Study of Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:375 (Feb.) 1932.

57. Weil, A., and Luhan, J. A.: The Demonstration of Myelolytic Substances in the Urine of Patients with Disseminated Sclerosis, Arch. Neurol. & Psychiat. **34**:459 (Aug.) 1935.

58. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

59. (*a*) Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931. (*b*) Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, Arch. Neurol. & Psychiat. **41**:1087 (June) 1939.

60. Putnam, T. J.: Studies in Multiple Sclerosis: "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**: 929 (May) 1935.

61. Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:799 (April) 1938.

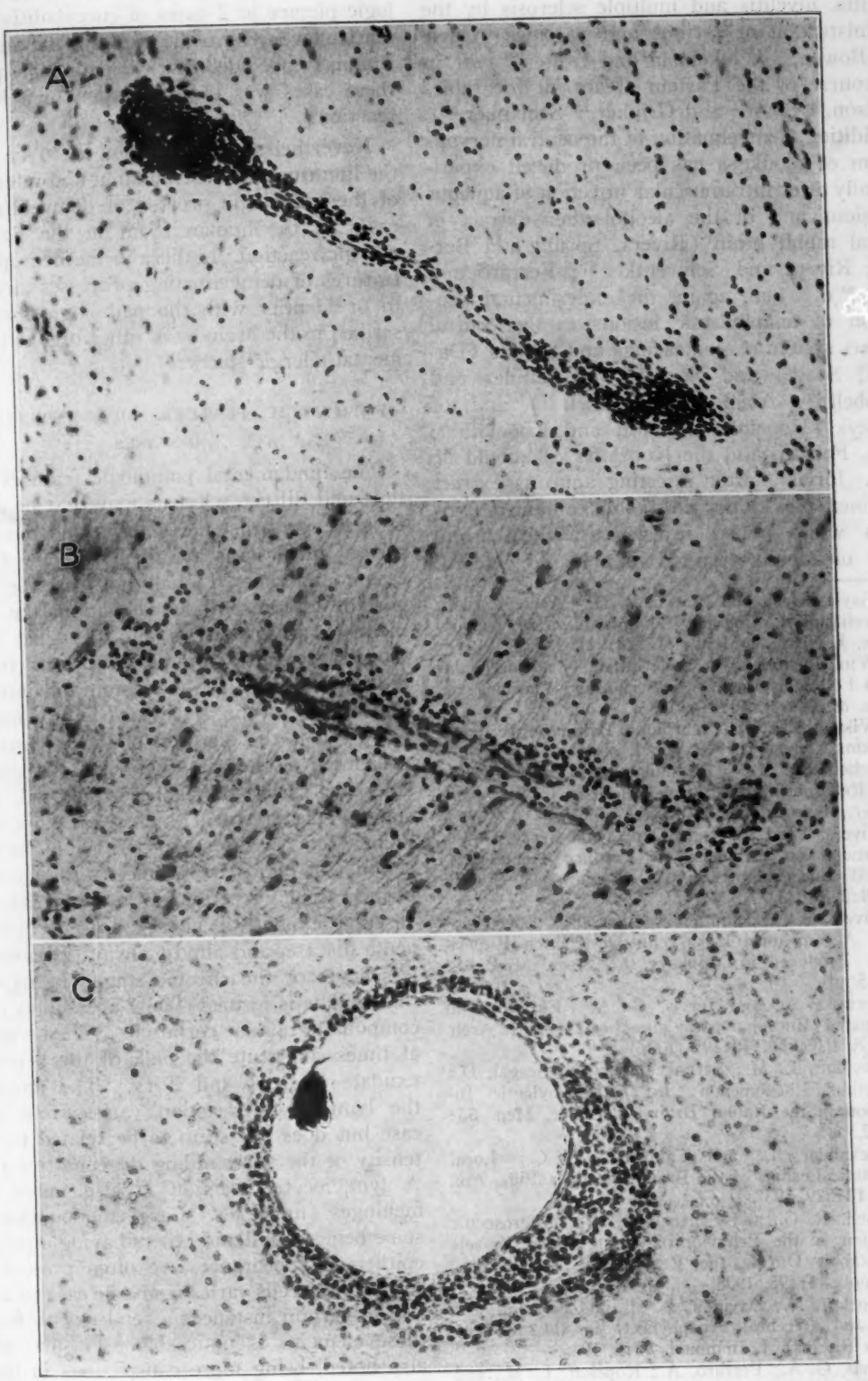


Fig. 1.—Blood vessels surrounded by lymphocytic reactions of various intensities. *A*, Nissl stain; *B* and *C*, hematoxylin and eosin stain.

the literature of the precipitation of encephalomyelitis, myelitis and multiple sclerosis by the administration of serums and vaccines (Gayle and Bowen,[62] Winkelman and Gotten[63]) or in the course of the Pasteur treatment for rabies (Wilson,[64] Bassoe and Grinker,[23] Scheinker[65]). In addition, demyelination of the central nervous system of monkeys has been produced experimentally after intramuscular injection of aqueous emulsions and of the alcohol-ether extract of normal rabbit brain (Rivers, Sprunt and Berry[66]; Rivers and Schwentker[67]; Ferraro and Jervis[68]). Then, again, the experimental production of anaphylactic lesions in the central nervous system of guinea pigs and rabbits (Davidoff, Seegal and Seegal[69]; Alexander and Campbell[70]; Abell and Schenck[71]) and of monkeys (Kopeloff, Davidoff and Kopeloff[72]; Jervis, Ferraro and the Kopeloffs[73]) should be noted. Jervis[74] after injecting aqueous extract of guinea pig kidney in rabbits obtained antibodies which when injected in the carotid artery of rabbits resulted in areas of cerebral demyelination. Recently I[75] described the pathologic picture in 2 cases of encephalitis following scarlet fever; from the study of the vascular reaction, I concluded that the pathologic process in these cases was the expression of a hyperergic reaction.

Neverthelss, no discussion is to be found in the literature of the evaluation and interpretation of the pathologic process of demyelinating diseases in the human brain in the light of an allergic reaction. Is there in the neuropathologic features of demyelinating processes any analogy to or identity with the pathologic features described in the brain or in other organs in experimental allergic states?

PATHOLOGIC FEATURES OF DEMYELINATING DISEASES

The fundamental pathologic features of multiple and diffuse sclerosis may first be analyzed. It is accepted that the severity and the distribution of the lesions are likely to vary from one case to another. I shall not describe the important features of demyelination, the involvement of axis-cylinders and the glial reaction. No disagreement seems to exist with respect to the variability in the extension and intensity of the loss of myelin sheaths. Slightly more controversial is the question of the intensity of involvement of the axis-cylinders. Although considerable variation has been reported, no substantial disagreement seems to exist on this point. Universally accepted, also, is the glial reaction. Of major importance is the controversy of the vascular reaction. In my experience, perivascular exudate is always present in cases of acute disease, and almost always in cases of the less acute or the chronic stage. In most cases the exudate is formed chiefly of lymphocytes and compound granular corpuscles. The lymphocytes at times constitute the bulk of the perivascular exudate (figs. 1 and 2 *A*). The intensity of the lymphocytic reaction varies from case to case but does not seem to be related to the intensity of the surrounding degenerative process. A lymphocytic reaction is also noted in the meninges (fig. 2 *B*). Large mononuclear cells, some being round and others having a polygonal, epithelioid appearance, are often present. The size of these cells varies from one case to another, and in certain instances a tendency to fusion of these elements is noticeable. Plasma cells are also noted, being more conspicuous in the very acute stage or in areas in which the pathologic

62. Gayle, R. F., and Bowen, R. H.: Acute Ascending Myelitis Following the Administration of Typhoid Vaccine, J. Nerv. & Ment. Dis. **78**:221, 1933.

63. Winkelman, N. W., and Gotten, N.: Encephalomyelitis Following the Use of Serum and Vaccine, Am. J. Syph. & Neurol. **19**:414, 1935.

64. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1, p. 166.

65. Scheinker, M.: Disseminated Encephalomyelitis and Its Relationship to Multiple Sclerosis, J. Neuropath. & Exper. Neurol. **2**:418, 1943.

66. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**:39, 1933.

67. Rivers, T. M., and Schwentker, F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**: 689, 1935.

68. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

69. Davidoff, L. M.; Seegal, B. C., and Seegal, D.: The Arthus Phenomenon: Local Anaphylactic Inflammation in the Rabbit Brain, J. Exper. Med. **55**: 163, 1932.

70. Alexander, L., and Campbell, A. C.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229, 1937.

71. Abell, R. G., and Schenck, H. P.: Microscopic Observation on the Behavior of Living Blood Vessels of the Rabbit During the Reaction of Anaphylaxis, J. Immunol. **34**:195, 1938.

72. Kopeloff, N.; Davidoff, L. M., and Kopeloff, L.: General and Cerebral Anaphylaxis in the Monkey (Macacus Rhesus), J. Immunol. **30**:6, 1936.

73. Jervis, G. A.; Ferraro, A.; Kopeloff, L. M., and Kopeloff, N.: Neuropathologic Changes Associated with Experimental Anaphylaxis in Monkeys, Arch. Neurol. & Psychiat. **45**:733 (May) 1941.

74. Jervis, G. A.: Forssman's "Carotid Syndrome," Arch. Path. **35**:560 (April) 1943.

75. Ferraro, A.: Allergic Brain Changes in Post-Scarlatinal Encephalitis, J. Neuropath. & Exper. Neurol. **3**:239 (July) 1944.

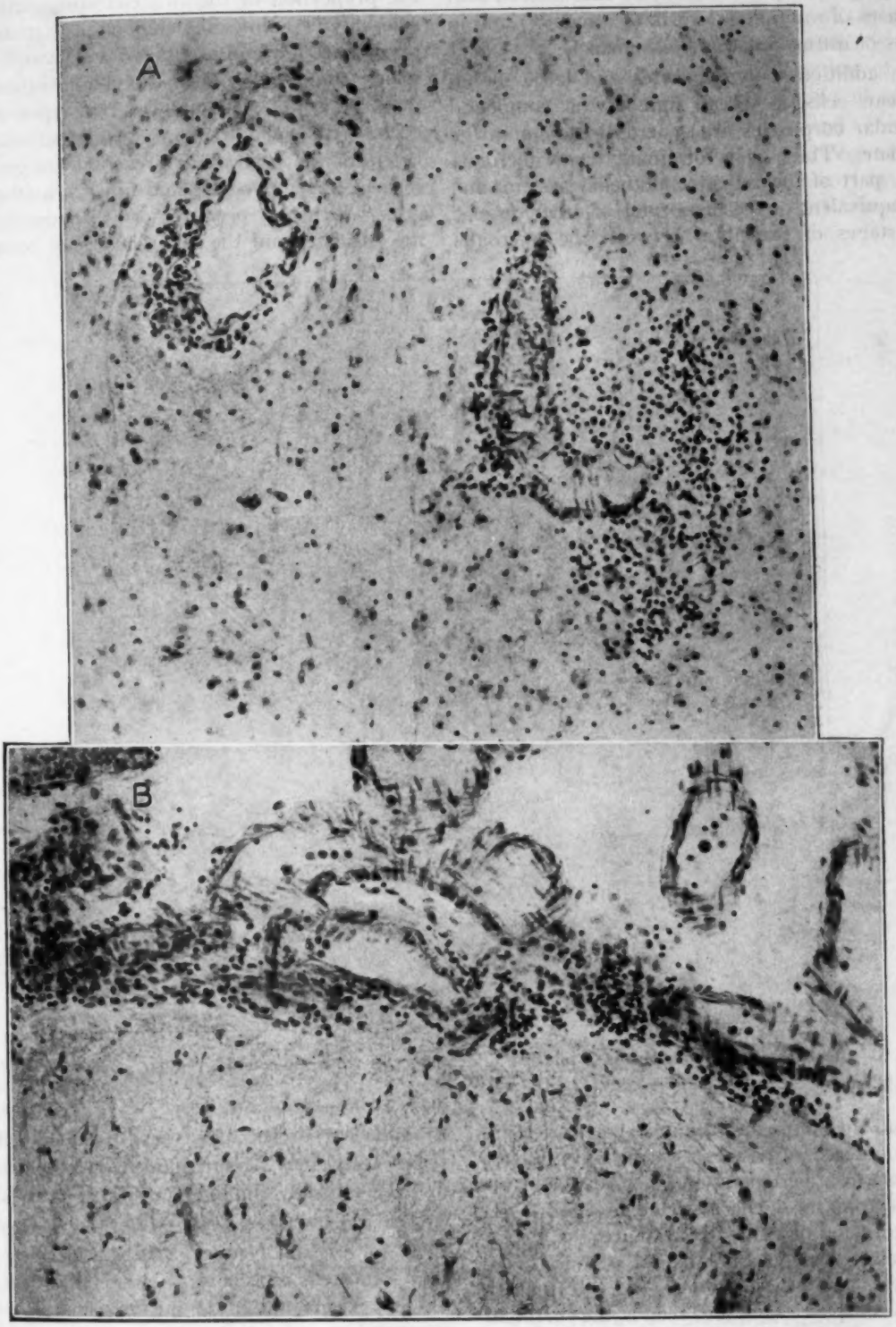


Fig. 2.—*A*, perivascular reaction consisting predominantly of lymphocytes on the right side. The infiltration of the blood vessel on the left is mild. *B*, lymphocytic reaction in the meninges, with no appreciable degeneration of the cerebral cortex. Hematoxylin and eosin stain.

process is severe. Polymorphonuclear elements, though generally absent, may be encountered both in cases of multiple sclerosis (Putnam [76]) and in cases of diffuse sclerosis (Bouman [8]).

In addition to lymphocytes and large mononuclear cells, a great number of compound granular corpuscles are generally present in the exudate. These cells originate from microglia cells, part of the reticuloendothelial system, and the equivalent of the histiocytes of other organs. All stages of transition between the microglia and histiocytes is noticeable. In such an event the proportion of the two elements varies considerably. At times the compound granular corpuscles are few and are mixed with lymphocytes, which stand out in hematoxylin-eosin preparations (fig. 3). At times the two types of cells occur with equal frequency, and the innermost layers of the perivascular reaction are generally formed of lymphocytes and other hematogenous cells, which may occupy more than one layer of the exudate, and the outer layers of compound

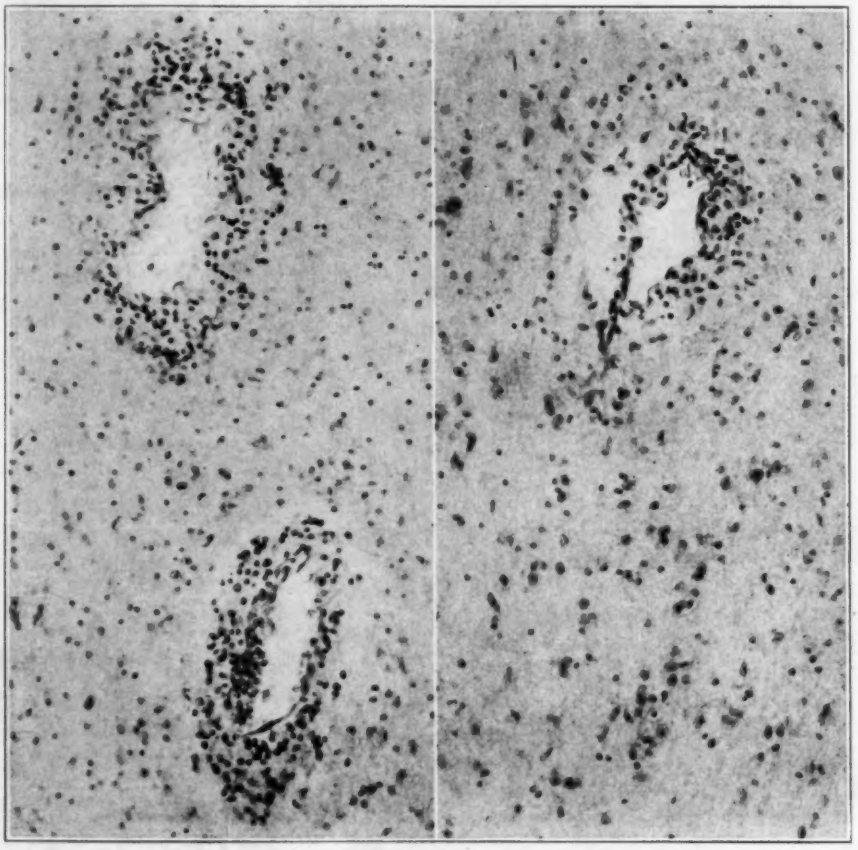


Fig. 3.—Blood vessels surrounded by a mixture of lymphocytes and compound granular corpuscles. Hematoxylin and eosin stain.

cells and the compound granular corpuscles may be encountered. At times the microglia cells are in a state of hypertrophy and, before vacuolation of the cytoplasm, when collected in a mass, give the impression of a mosaic structure, the appearance being analogous to that of a collection of histiocytes in other organs. Free compound granular corpuscles are also seen in the surrounding tissue. Often a combination of lymphocytes granular corpuscles. Occasionally one pole of the blood vessel may be surrounded by lymphocytes and the other by compound granular corpuscles.

The walls of the blood vessels themselves are more or less involved, and their thickening has been reported, especially in the smaller vessels. Hyaline degeneration is not uncommon. One needs only to refer to the observations of Putnam and Alexander [59b] to appreciate the frequency and importance of thrombus formation.

Necrotic areas may be present, especially in the very acute stage or with reactivation of the

76. Putnam, T. J.: Studies in Multiple Sclerosis: Similarities Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, Arch. Neurol. & Psychiat. **35**:1289 (June) 1936.

disease. Capillary hemorrhages have also been described (Siemerling and Raecke[77]). More often, congestion of blood vessels is present either in the parenchyma or in the meninges (fig. 4). Thickening of the meninges is not uncommon. Edema is also noted, especially in the acute stage, either in the parenchyma or in the perivascular spaces (fig. 5).

In diffuse sclerosis there is the same fundamental histologic picture. Even in cases in which the process has been considered degenerative a small amount of perivascular infiltration has often been reported. In cases in which the disease is openly considered inflammatory the perivascular reaction, which is generally intense, is similar to that of multiple sclerosis. In some instances there is a cuffing of lymphocytes, and in others, a cuffing of compound granular corpuscles, often with a mixture of the two types which are distributed as in multiple sclerosis. Among the lymphocytes, the presence of large hematogenous mononuclear cells has also been reported; they have been called polyblasts (Schröder[78] and Henneberg[79]), large mononuclear cells of the tissues, or histiocytes (Eisner[80]), macrophages (Hermel[81]) and epithelioid elements rich in protoplasm (Creutzfeld[82]). Thickening of the blood vessel walls and new formation of capillaries (Kogerer,[83] Bielschowsky and Henneberg,[11] Marie and Foix[4]) have also been noted. An increase in mesenchyme has also been reported (Neubürger,[12] Klarfeld,[84] Weimann,[16]

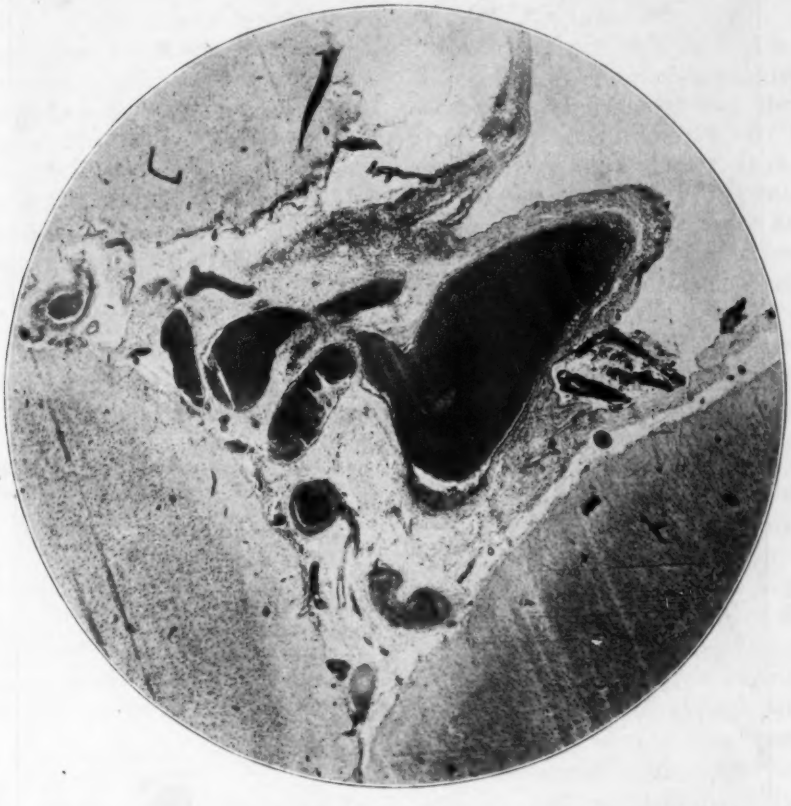


Fig. 4.—Marked congestion of the meningeal blood vessels. Hematoxylin and eosin stain.

77. Siemerling, E., and Raecke, J.: Zur pathologische Anatomie und Pathogenese der multiplen Sklerose, Arch. f. Psychiat. **53**:385, 1914.

78. Schröder, P.: Encephalitis und Myelitis: Zur Histologie der Kleinzelligen Infiltration im Nervensystem, Monatschr. f. Psychiat. u. Neurol. **94**:87, 1918.

79. Henneberg, cited by Bouman.[3]

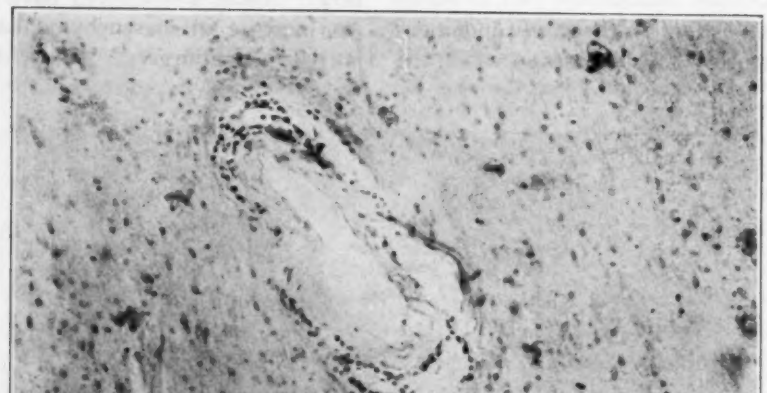
80. Eisner, W.: Ueber einen Fall von herdformig disseminierter Sklerose des Gehirns bei einem Saugling, Virchows Arch. f. path. Anat. **248**:153, 1924.

81. Hermel, H., cited by Bouman.[3]

82. Creutzfeld, H. G.: Ueber eine eigenartige herdformige Erkrankung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **57**:1, 1920.

83. Kogerer, H.: Beitrag zur Kenntnis der Encephalitis-periaxialis diffusa, Jahrb. f. Psychiat. **95**:109, 1927.

84. Klarfeld, B.: Zur Frage der subakut verlaufenden diffusen Erkrankungen des Hemisphärenmarkes, Allg. Ztschr. f. Psychiat. **129**:294, 1923.



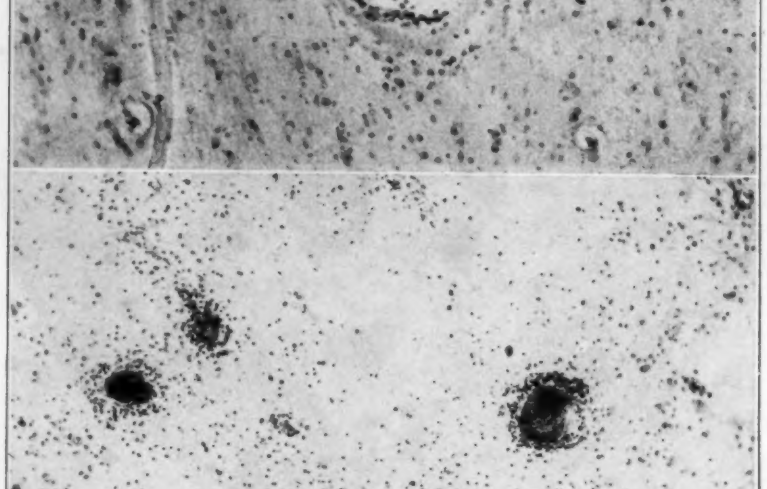


Fig. 5.—Perivascular edema and free edema in the parenchyma.

Bouman[3] and Bielschowsky and Maas[85]). Hemorrhages were observed by Gagel[86]; Grainger-Stewart, Greenfield and Blandy[87]; Schaltenbrand[88]; Schröder[78]; Bouman[3]; Flatau,[89] and Kraus and Weil.[5] Necrotic areas and cystic degeneration were reported by Schilder,[90] Barré and associates,[91] Bodechtel and Guttmann,[92] Bouman,[3] Bielschowsky and Henneberg,[11] Wohlwill,[93] Marburg[94] and Gerstmann and Straussler.[95]

Of the pathologic changes of both multiple and diffuse sclerosis, one detail of the process which, in the light of the present investigation, seems important has been underemphasized, namely, the presence of giant cells in the areas of demyelination. These cells have been described by various authors. Neubürger[96] observed them free in the tissue or surrounding the blood vessels in a case of infantile multiple sclerosis (fig. 6 *A* and *B*) and concluded that they were of mesodermic origin; he illustrated their derivation from adventitial cells. These cells do not contain lipid material.

Creutzfeld,[97] in a case of acute multiple sclerosis of fifteen months' duration in a 15 year old girl, described multinucleated giant cells which he asserted to be of glial origin. Hallervorden,[98] in a case of a demyelinating disease of only five or six weeks' duration in a man aged 24, reported the presence of giant cells, which they also claimed to be of glial origin. Peters,[99] in 2 cases of encephalomyelitis, of approximately six weeks' and six months' duration respectively, which he found difficult to differentiate from multiple sclerosis, described giant cells in which he detected karyorrhexis. He predicated their origin from glia cells, though he never actually saw transitional stages between the macrogliocytes and the giant cells.

Hallervorden,[98] in a case of a disease which he concluded to be nonsuppurative disseminated encephalomyelitis, described the presence of giant cells of glial origin (fig. 6 *C*). Eisner,[80] in a case of disseminated sclerosis in an infant aged 4½ months, described the presence of giant cells not only in the brain but in the lungs and stated that their origin was probably from mesodermic elements presumably blood vessel walls.

Collier and Greenfield,[100] in a case of a child aged 5 years with diffuse sclerosis of fifteen months' duration, described in areas of "diffuse demyelination" the presence of large globoid cells with multiple nuclei under the capsule of the cell, arranged as a chain of thin, flattened structures. The authors concluded that these cells were of glial origin, foreign to most other forms associated with destruction of myelin, and stated the belief that they formed a prominent, and possibly an essential, feature of diffuse sclerosis.

Scherer[101] stated his opinion that a case of patchy sclerosis of seven months' duration, in which associated with typical patchy demyelination there were what he called neoplastic features, might represent a transition between multiple sclerosis and glioblastoma. Here, also, were numerous giant cells (figs. 7 *A* and *B*), which the author related to the glioblastic features of the process.

De Lange,[102] in a case of so-called Krabbe disease (diffuse infantile familial cerebral

85. Bielschowsky, M., and Maas, O.: Ueber diffuse und multiple Sklerose, J. f. Psychol. u. Neurol. **44**:138, 1932.

86. Gagel, O.: Zur Frage der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:418, 1927.

87. Grainger-Stewart, T.; Greenfield, J. G., and Blandy, M. A.: Encephalitis Periaxialis Diffusa: Report of Three Cases with Pathological Examinations, Brain **50**:1, 1927.

88. Schaltenbrand, G.: Encephalitis Periaxialis Diffusa (Schilder), Arch. Neurol. & Psychiat. **18**:944 (Dec.) 1927.

89. Flatau, E.: Encephalopathia scleroticans progressiva, Encéphale **20**:475, 1925.

90. Schilder, P.: Die Encephalitis periaxialis diffusa, Arch. f. Psychiat. **121**:327, 1924.

91. Barré, Morin, Draganesco and Reys: Encéphalite periaxiale diffusa (type Schilder), Rev. neurol. **2**:541, 1926.

92. Bodechtel, G., and Guttmann, E.: Zur Pathologie und Klinik diffiusen Markerkrankungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:544, 1932.

93. Wohlwill, F.: Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

94. Marburg, O.: Multiple Sklerose, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 546.

95. Gerstmann, J., and Straussler, E.: Zur Problemgebiet der Encephalomyelitis und der multiplen Sklerose, Arch. f. Psychiat. **93**:182, 1931.

96. Neubürger, K.: Zur Histopathologie der multiplen Sklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. **76**:384, 1922.

97. Creutzfeld, H. G.: Zur Frage der sogenannten akuten multiplen Sklerose, Arch. f. Psychiat. **68**:484, 1923.

98. Hallervorden, J.: Eigenartige und nicht rubrizierbare Prozesse, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, p. 1063.

99. Peters, G.: Zur Frage der Beziehungen zwischen der disseminierten nichteitrigen Encephalomyelitis und der multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:356, 1935.

100. Collier, J., and Greenfield, J. G.: The Encephalitis Periaxialis of Schilder: A Clinical and Pathological Study, Brain **47**:489, 1924.

101. Scherer, H. J.: La "Glioblastomatose en plaques," J. belge de neurol. et de psychiat. **38**:1, 1938.

102. de Lange, C.: Ueber die familiäre infantile Form der diffusen Gehirnsklerose (Krabbe), Ann. pædiat. **154**:140, 1940.

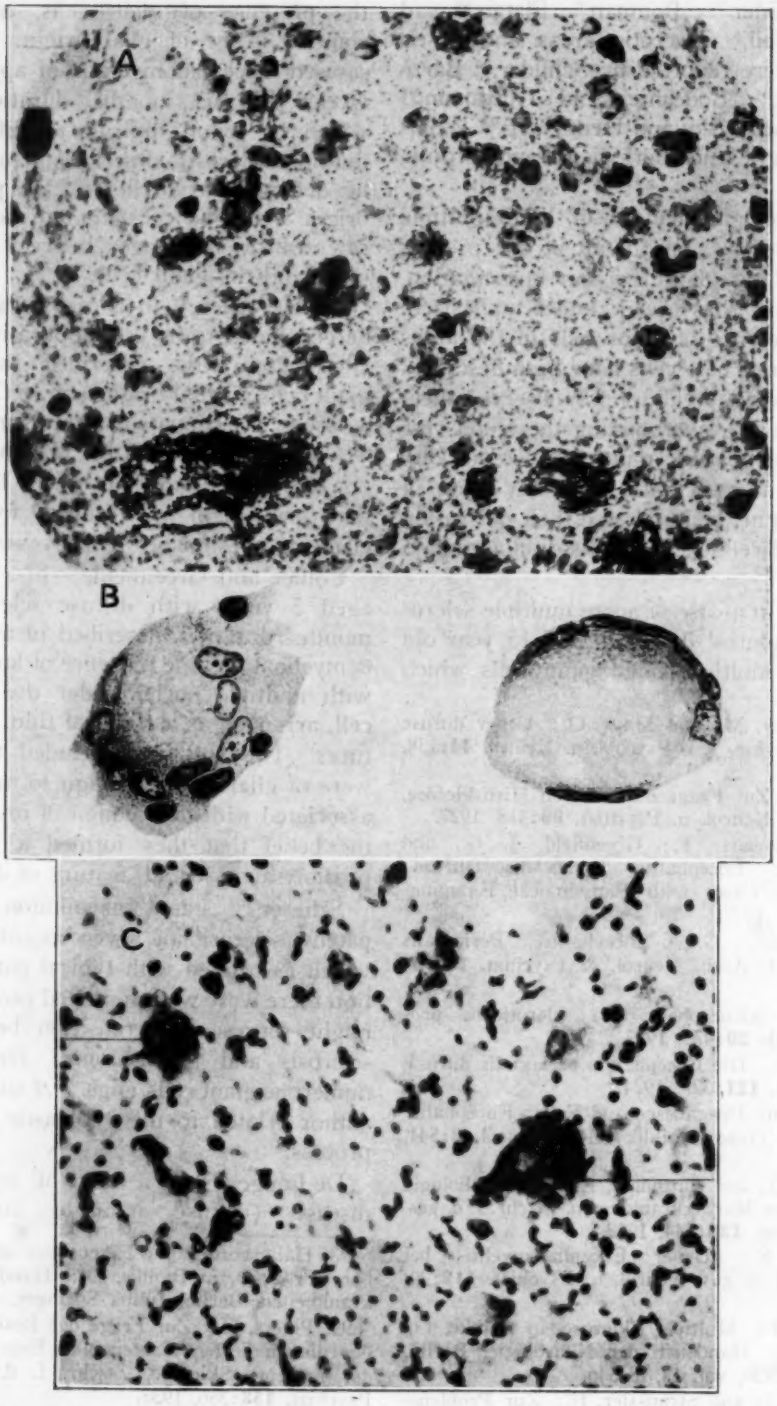


Fig. 6.—*A*, and *B*, giant cells in the parenchyma of the brain and details of giant cells in a case of multiple sclerosis (from Neubürger [96]); *C*, giant cells in the parenchyma of the brain in a case of demyelinating disease (from Hallervorden [98]).

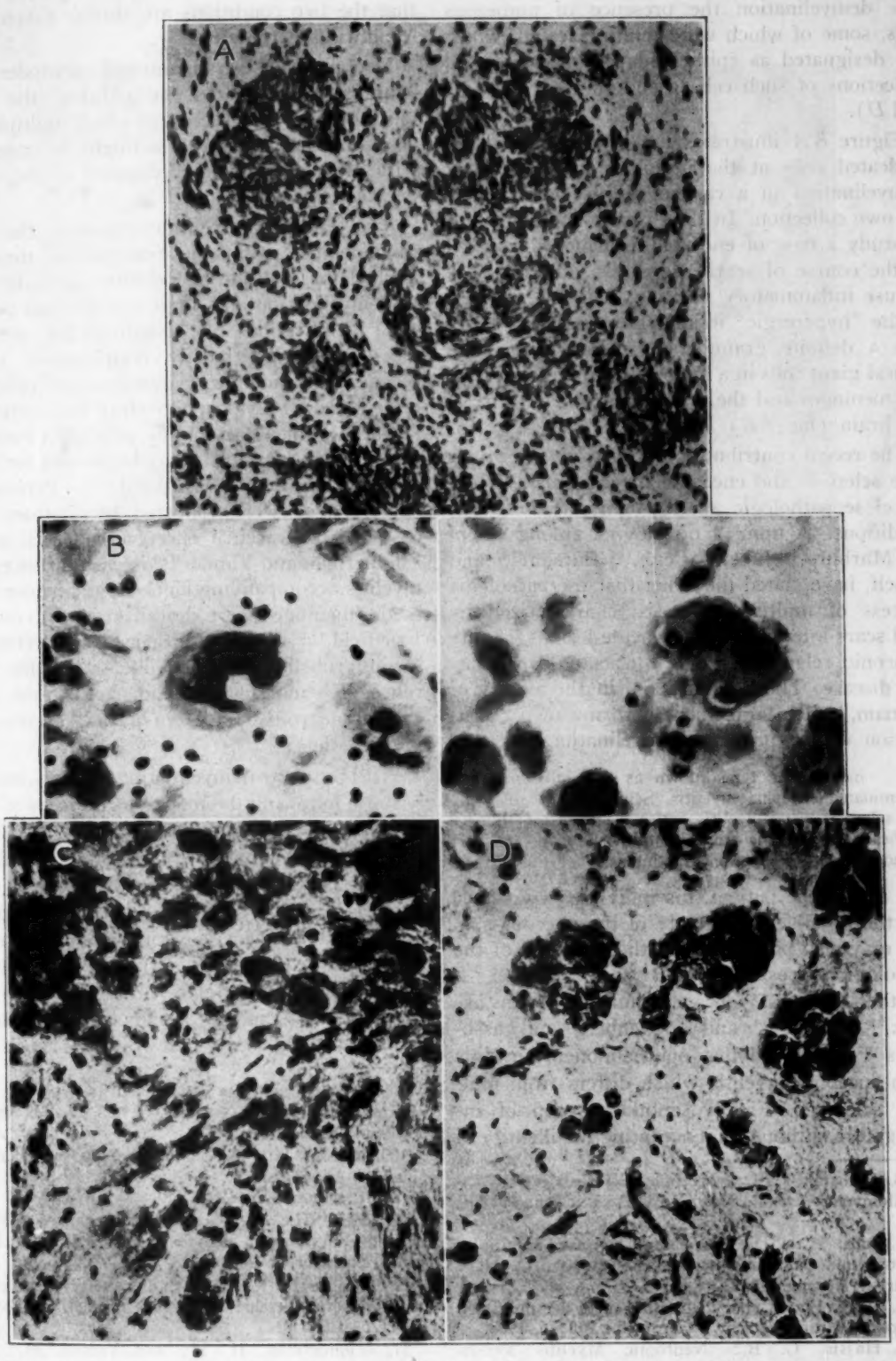


Fig. 7.—*A* and *B*, tumor nodules and details of cells in a case of multiple sclerosis (from Scherer [101]); *C* and *D*, giant epithelioid cells and pseudotumor formation in a case of Krabbe's disease (diffuse infantile familial cerebral sclerosis (from de Lange [102]).

sclerosis), described in association with the diffuse demyelination the presence of numerous cells, some of which were multinucleated, which she designated as epithelioid cells. She termed collections of such cells pseudotumors (fig. 7 *C* and *D*).

Figure 8 *A* illustrates the presence of multinucleated cells at the periphery of a patch of demyelination in a case of diffuse sclerosis in my own collection. In 1944 I had the opportunity to study a case of encephalitis which developed in the course of scarlet fever. In addition to a diffuse inflammatory reaction, which I ascribed to the "hyperergic" inflammatory process, there was a definite granulomatous formation, with typical giant cells in a limited area involving both the meninges and the underlying parenchyma of the brain (fig. 8 *B*).

The recent contribution of Putnam [103] on multiple sclerosis and encephalomyelitis makes clear the close pathologic analogy between these two conditions. A number of authors, among whom are Marburg,[34] Juba,[104] Pette,[105] Putnam [103] and myself, have stated the belief that the pathologic process of multiple sclerosis, characterized by glial scars interspersed with acute lesions, is only a chronic, relapsing form of the acute demyelinating disease. These conditions, in the words of Putnam, and in agreement with my own classification of the primary demyelinating diseases,

> . . . include the type known as post-infectious and disseminated encephalomyelitis, Schilder's diseases, diffuse sclerosis, neuromyelitis optica. The histopathology of these disorders is fundamentally uniform, the differences being in location and intensity of the lesions.

The age of the patient, his individual resistance and the possible immaturity of the nervous system may also play a role in the diffusion of the pathologic process.

Other authors, however, among whom are Beck,[21] Hassin [106] and Lowenberg and associates [107] concluded that ophthalmoneuromyelitis is an encephalomyelitis which differs from multiple sclerosis. Finally, another group of investigators, although not accepting the identity of multiple sclerosis and encephalomyelitis, stated that the two conditions are similar (Anton and Wohlwill,[17] Creutzfeld [82]).

Neubürger,[108] Gerstmann and Straussler [95] and Marcus [109] considered, in addition, the possibility of a mixed process, in which multiple sclerosis or encephalomyelitis might be associated with other inflammatory diseases of the central nervous system.

The encephalomyelitides present the same fundamental pathologic features as those described for multiple and diffuse sclerosis: areas of demyelination and often vascular and perivascular infiltration of hematogenous elements. These cells are mostly lymphocytes, though plasma cells and large mononuclear cells have been noted. Polymorphonuclear leukocytes constitute at times part of the exudate (Pette [110]). The inflammatory cells may be present for only a short time (Pette,[110] Walthard [111]). Perivascular hemorrhages were reported by Putnam [103] in cases of postvaccinal encephalomyelitis, and by Zimmerman and Yannet [112] in cases of encephalomyelitis accompanying chickenpox; hemorrhages in the meninges were described by Davison and Friedfeld [113] in cases of encephalomyelitis following rubella. Figure 9 illustrates the occurrence of hemorrhage in the parenchyma of the central nervous system in a case occurring in my experience.

With the acute demyelinating diseases, especially those following the infectious diseases of childhood, as with multiple and diffuse sclerosis, a pronounced microglial reaction surrounds the blood vessels and is often associated with a cuffing of lymphocytes. This histiocytic reaction, as a matter of fact, constitutes an outstanding pathologic feature (fig. 10). Thrombi of small venules have been described especially by Putnam and Alexander,[59b] and Kreider also encountered them in my cases of encephalitis com-

103. Putnam, T. J.: Multiple Sclerosis and "Encephalomyelitis," Bull. New York Acad. Med. **19**:301, 1943.

104. Juba, A.: Die Beziehung zwischen multipler Sklerose und Encephalomyelitis disseminata, Deutsche Ztschr. f. Nervenh. **143**:268, 1937.

105. Pette, H.: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **105**:76, 1928.

106. Hassin, G. B.: Neuroptic Myelitis Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **37**:1083 (May) 1937.

107. Lowenberg, K.; DeJong, R. N., and Foster, D. B.: Neuromyelitis Optica, Tr. Am. Neurol. A. **67**:59, 1941.

108. Neubürger, K.: Encephalitis epidemica bei multipler Sklerose, Zentralbl. f. d. ges. Neurol. u. Psychiat. **33**:515, 1923.

109. Marcus, H.: Encephalitis lethargica, Sclérose en plaques: Eine differential diagnostische Studie, Acta psychiat. et neurol. **5**:129, 1930.

110. Pette, H.: Postvaccinole Encephalitis, in Bunke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 259.

111. Walthard, K.: Spatstadium einer Enzephalitis nach Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **134**:176, 1930.

112. Zimmerman, H. M., and Yannet, H.: Nonsuppurative Encephalomyelitis Accompanying Chickenpox, Arch. Neurol. & Psychiat. **26**:322 (Aug.) 1931.

113. Davison, C., and Friedfeld, L.: Acute Encephalomyelitis Following German Measles, Am. J. Dis. Child. **55**:496 (March) 1938.

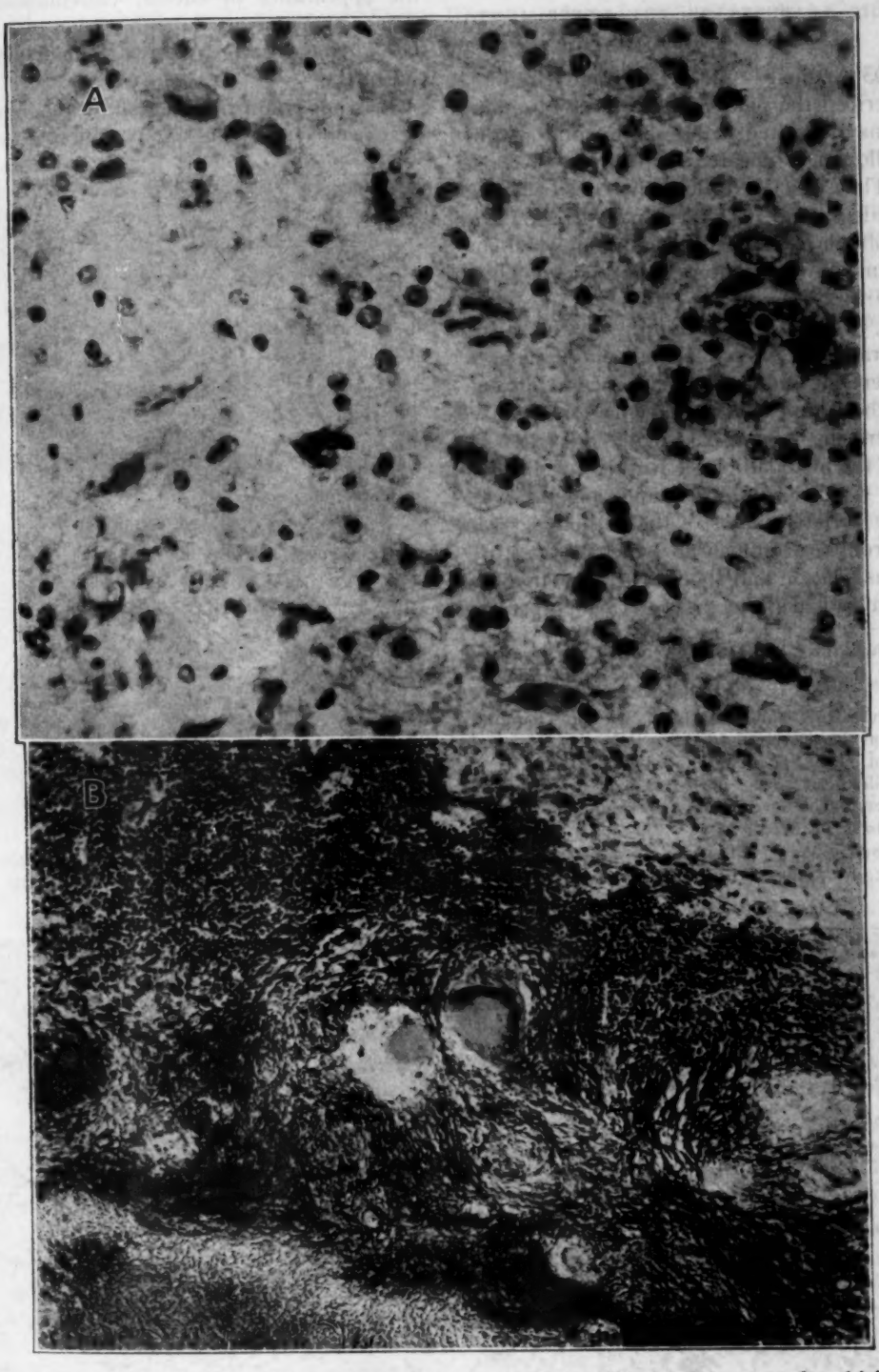


Fig. 8.—*A*, multinucleated cells at the periphery of an area of demyelination in a case of multiple sclerosis; hematoxylin and eosin stain. *B*, giant cells at the periphery of a granulomatous formation in a case of scarlet fever encephalitis (from Ferraro [75]); Van Gieson stain for connective tissue.

plicating measles. Edema, degeneration of the vascular walls and necrosis are also present.

HISTOLOGIC FEATURES OF THE EXPERIMENTAL ALLERGIC REACTION

In 1903 Arthus [114] and Arthus and Breton [115] first described the pathologic features of cutaneous lesions associated with experimental anaphylaxis following repeated injections of horse serum. They described the occurrence of hemorrhages, edema and perivascular infiltration with polymorphonuclear cells, a condition which has since been known as the "Arthus phenomenon" (Nicolle).

Rössle,[116] in 1914, elaborating on the pathologic character of such a phenomenon, spoke of the "hyperergic" inflammatory reaction, in contrast to the normergic reaction of nonsensitized skin. Gerlach,[117] in 1923, made an extensive report on the histopathologic features of this condition in rabbits, rats and guinea pigs and followed the various phases of the pathologic reaction in groups of animals in which he had produced sensitization and shock with various doses of antigen and in the course of various periods. Gerlach confirmed the fundamental statements of Arthus, Breton and Rössle with regard to the appearance of edema, vasodilation, hemorrhages and perivascular infiltration of leukocytes. Hemorrhages were more pronounced in the subcutis.

It is important to note that in the course of the first twenty-four hours no lymphocytes were seen

114. Arthus, M.: Injections répétées de sérum de cheval chez le lapin, Compt. rend. Soc. de biol. **55**:817, 1903.

115. Arthus, M., and Breton: Lesions cutanées produites par les injections de serum de cheval chez le lapin, Compt. rend. Soc. de biol. **55**:1479, 1903.

116. Rössle, R.: Ueber die Merkmale der Entzündung im allergischen Organismus, Verhandl. d. deutsch. path. Gesellsch. **17**:281, 1914.

117. Gerlach, W.: Studien über hyperergische Entzündung, Virchows Arch. f. path. Anat. **247**:294, 1923.

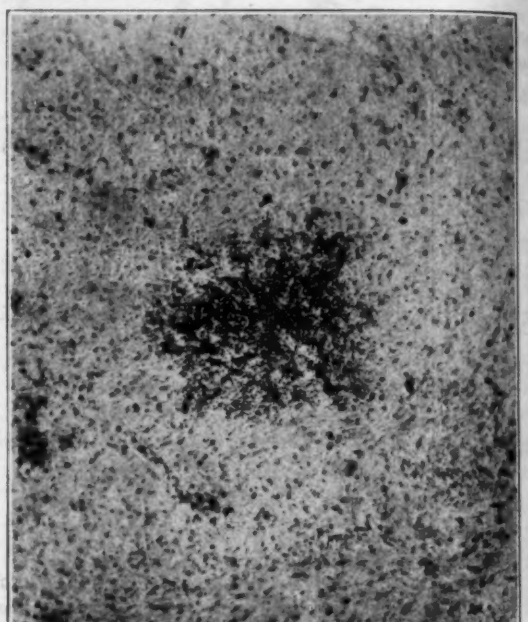


Fig. 9.—Hemorrhage in the nerve parenchyma in a case of acute disseminated encephalomyelitis. Hematoxylin and eosin stain.

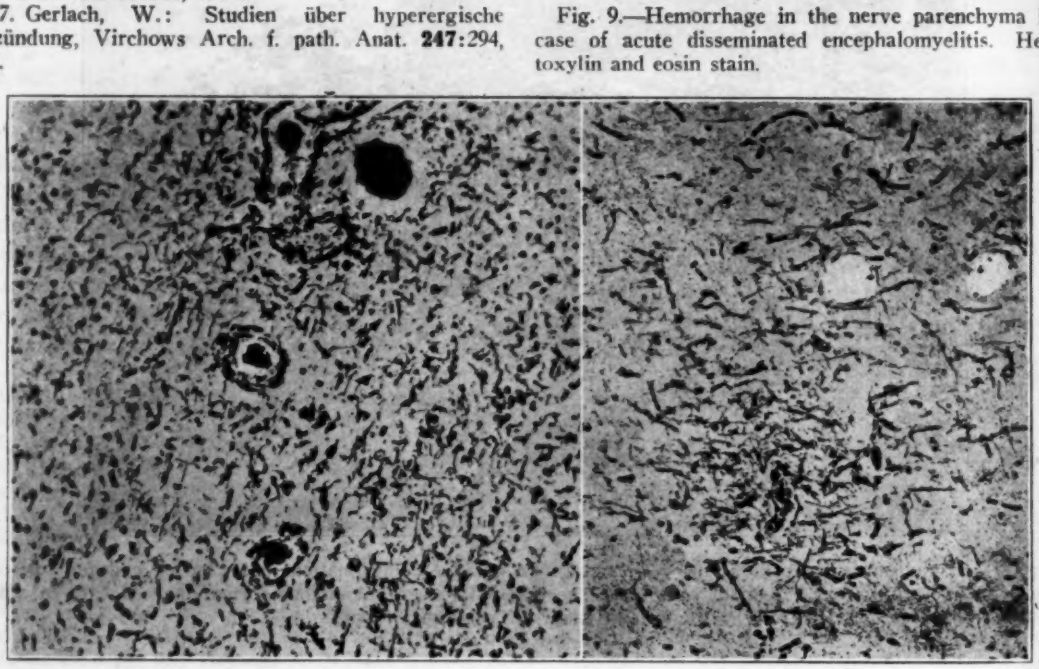


Fig. 10.—Pronounced perivascular histiocytic reaction in a case of measles encephalitis; Globus-Penfield modification of Hortega's method for microglia.

in the perivascular infiltration or free in the tissues, though the walls of blood vessels were already seen to be undergoing necrotic changes. Soon after the end of twenty-four hours thrombus formation could be seen, with fibrin-forming exudate pouring from the necrotic walls of blood vessels. Thirty-four hours later lymphocytes and large mononuclear cells were present in the exudate, where multinucleated elements had already made their appearance. Forty-one hours later loose adventitial cells and fibroblasts were noted. Four days later numerous mobile cells, arising partly from connective tissue and partly from the adventitia, were noticed, and eight days later the cicatricial process of repair was prominent, with considerable neoformation of fibroblasts.

Gerlach stated that vascular spasm may occur, that the hemorrhages may be the result of stasis, that the presence of fibrin varies from one region to another, the amount being scant in the skin of the back and abundant in the skin of the ear, and that the pure "Arthus phenomenon" is expressed by hemorrhages and exudation of leukocytes, whereas the subsequent mobilization of histiocytes is presumably the result of local reaction to the antigen previously injected. A minimum dose of the antigen is necessary to produce the Arthus phenomenon, which Gerlach asserted to be the expression of a general reaction of wide significance.

In 1929 Klinge,[118] elaborating on the original statements by Weintrand and Stettner[119] that articular rheumatism and polioarthritis in children were the expression of an allergic reaction of the joints, began an extensive study of tissue anaphylaxis in these areas. His investigations have considerable importance because of the fundamental conclusion that in experimental local anaphylaxis a transformation of the histologic picture can be detected in relation to the dose of the antigen and to the time element. In the early stages of the anaphylactic reaction following large doses of antigen and repeated sensitization to the vascular reaction was a stormy leukocytic phenomenon associated with hemorrhage (Arthus phenomenon). With smaller amounts of antigen and more protracted sensitization a reaction was produced in which both leukocytes and mononuclear cells participated. After more protracted sensitization in the course of many months, the histologic reaction underwent a total change from a polymorphonuclear to a monocytic-histiocytic type, without further participation of polymorphonuclear cells, but with an occasional tendency to granulomatous formation. Thus Klinge confirmed conclusions which Graff[120] had already substantially reached in 1927.

Klinge's work was followed by studies by other investigators, among whom were Vaubel,[121] Knepper,[122] Knepper and Waaler[123] and Epstein.[124] These authors were concerned especially with such factors as tissue and organ susceptibility to anaphylactic reaction and the importance of various precipitating factors in determining the hyperergic inflammatory reactions. Of these factors, trauma, hyperventilation, overexertion, heat and cold and the influence of various hormones and cytotoxins were studied.

In general, these authors confirmed the histopathologic observations of Klinge, particularly with respect to the occurrence of granulomatous formations in the stage of the lymphocytic-histiocytic reaction. Necrosis of blood vessel walls, proliferation of the intima, formation of hyaline thrombi and hyperplasia of the lymphoid apparatus were also reported.

During investigations on the anaphylactic reaction of various organs, Rachmanow[125] noted degenerative alterations in the neuron cells of animals which had died in anaphylactic shock. Weinberg,[126] in cases of severe shock, reported perivascular infiltration, hemorrhages, occasional thrombosis, diffuse degenerative changes of neuron cells and alterations of the myelin sheaths. Feuillié and Thiers[127] produced shock by injecting intravenously into a dog five doses of Witte's peptone (0.1 Gm. per kilogram of body weight) over a period of two weeks, after which they reported lymphocytic infiltration of the pia at the level of the lumbar region but no changes in the

118. Klinge, F.: Die Eiweissüberempfindlichkeit (Gewebsanaphylaxie) der Gelenke, Beitr. z. path. Anat. u. z. allg. Path. **83**:185, 1929.

119. Weintrand and Stettner, cited by Klinge.[118]

120. Graff, S.: Rheumatismus infectiosus, Deutsche med. Wchnschr. **53**:708, 1927.

121. Vaubel, E.: Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindegewebes, Beitr. z. path. Anat. u. z. allg. Path. **89**:374, 1932.

122. Knepper, R.: Ueber die Lokalisierung der experimentellen allergischen Hyperergie, Virchows Arch. f. path. Anat. **296**:364, 1935.

123. Knepper, R., and Waaler, G.: Hyperergische Arteritis der Kranz- und Lungengefässe bei funktioneller Belastung, Virchows Arch. f. path. Anat. **294**:587, 1935; Lungenbefunde beim akuten anaphylaktischen Shock des Kaninchens, ibid. **296**:465, 1935.

124. Epstein, cited by Vaubel.[121]

125. Rachmanow, M.: Lésions nerveuses dans l'anaphylaxie séreuse et vermineuse, Compt. rend. Soc. de biol. **75**:317, 1913.

126. Weinberg, E.: Histologische Veränderungen im Gehirn wahrend des anaphylaktischen Shocks, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:451, 1923.

127. Feuillié, E., and Thiers, J.: Production expérimentale de sclérose dans le système nerveux, Rev. neurol. **1**:606, 1926.

nerve tissue proper. In guinea pigs, rabbits and dogs which died after anaphylactic shock Stief and Tokay[128] observed two types of diffuse lesions, vascular and parenchymatous. The former were essentially hemorrhagic and the latter degenerative. Garcin, Bertrand, Laplane and Frumusan[129] obtained no significant changes in the nervous system by repeated intravenous injections of horse serum. However, after repeated weekly injections of human serum in rabbits, 2 of 5 animals showed changes characterized by neuronophagia, meningeal infiltrations and scattered microglial nodules. Similar lesions were produced in the brains of guinea pigs in which human serum was repeatedly injected by the intraperitoneal route. Baginski, Czarnecki and Hurynowicz[130] produced sensitization and shock in 6 rabbits with horse serum injected by the intravenous and subcutaneous routes. Examination of the brain showed enlargement of the Robin-Virchow spaces and proliferation of adventitial cells. In addition, scattered throughout the brain, cerebellum and medulla were small necrotic foci, 0.04 to 0.1 mm. in diameter, consisting of necrotic nerve cells, proliferating microglia cells and occasional leukocytes and lymphocytes.

Subsequently, Davidoff, Seegal and Seegal[69] in rabbits prepared with multiple sensitizing injections of horse serum and subjected to shock by one intracerebral injection observed an extensive inflammatory lesion in the brain, characterized by edema, serous exudate, hemorrhages and leukocytic infiltration. It is of interest to note that, though without emphasis, there was mention in this study of the change in the type of vascular reaction occurring in the later periods of the experiment. If animals were allowed to survive five or six days after the last injection, the central area of the lesion was considerably shrunken and sharply demarcated from the rest of the brain. Although polymorphonuclear cells were still present, the perivascular cells had by this time been replaced largely with lymphocytes.

Alexander and Campbell,[70] using a single intraperitoneal injection of horse serum, followed by a second injection of the antigen intracerebrally, produced a lesion characterized by the presence of hemorrhages, vascular thrombosis, necrosis, demineralization, scavenger cells and a reaction of microglia cells, oligodendrocytes and astrocytes.

Tokushige,[131] after sensitization of rabbits by means of intracerebral injections of foreign serum, reported that a second intracerebral injection resulted in a local cerebral Arthus phenomenon, with a rise in cerebrospinal fluid pressure and no change in blood pressure.

Miyahara[132] demonstrated that injection of the protein antigen into the blood stream of allergized animals brings on hemorrhagic infarcts in the brain, while introduction into the cisterna causes leptomeningitis and "inflammation" of the blood vessels.

In monkeys (Macacus rhesus), prepared by intravenous injections of antigen, followed by injections of the same antigen into the cerebral veins, Kopeloff, Davidoff and Kopeloff[72] succeeded in obtaining a severe Arthus-like reaction, accompanied sometimes by contralateral motor symptoms. Necropsy revealed in 1 animal an area of hemorrhagic discoloration and softening about the sylvian fissure on the left side of the brain. There was generalized edema of the left hemisphere, and the entire midline seemed to be shifted to the right. No histologic description accompanied this report. In 1941 Jervis and I, in collaboration with the Kopeloffs,[73] reported on the neuropathologic changes associated with experimental anaphylaxis in the monkey.

A review of the neuropathologic investigation which I have undertaken since has established the following new factors concerned with the vascular changes and the transformation of the perivascular reaction in relation to the chronicity of the experiments. While in cases of the acute stage the reaction was of hemorrhagic type, associated with an exudate of polymorphonuclear cells, in the cases in which the experiments involved more chronicity the hemorrhagic component was absent and the exudate was fundamentally one of lymphocytes to which histiocytes were added.

A summary of the observations follows.

MONKEY 15.—This animal, which received five intravenous injections of egg white, 10 cc. each at two day intervals, followed fifteen days later by one intravenous injection (10 cc.) of the same antigen and, finally, fifteen days later by an intracerebral injection of 0.2 cc. of the same antigen, died within fifteen hours after the intracerebral injection with severe symptoms of collapse. Histologic examination disclosed considerable engorgement of the blood vessels, especially of veins

128. Stief, A., and Tokay, L.: Durch experimentelle Serumanaphylaxie verursachte Veränderungen des Nervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:715, 1934.

129. Garcin, R.; Bertrand, I.; Laplane, R., and Frumusan, P.: Sur certaines lesions histologiques du nevraxe consecutives aux chocs anaphylactiques, Compt. rend. Soc. de biol. **118**:1190, 1935.

130. Baginski, S.; Czarnecki, E., and Hurynowicz, J.: Lesions histologiques due système nerveux des lapins en etat anaphylactique, Compt. rend. Soc. de biol. **130**:567, 1939.

131. Tokushige, J., cited by Urbach and Gottlieb.[138]

132. Miyahara, K., cited by Urbach and Gottlieb.[138]

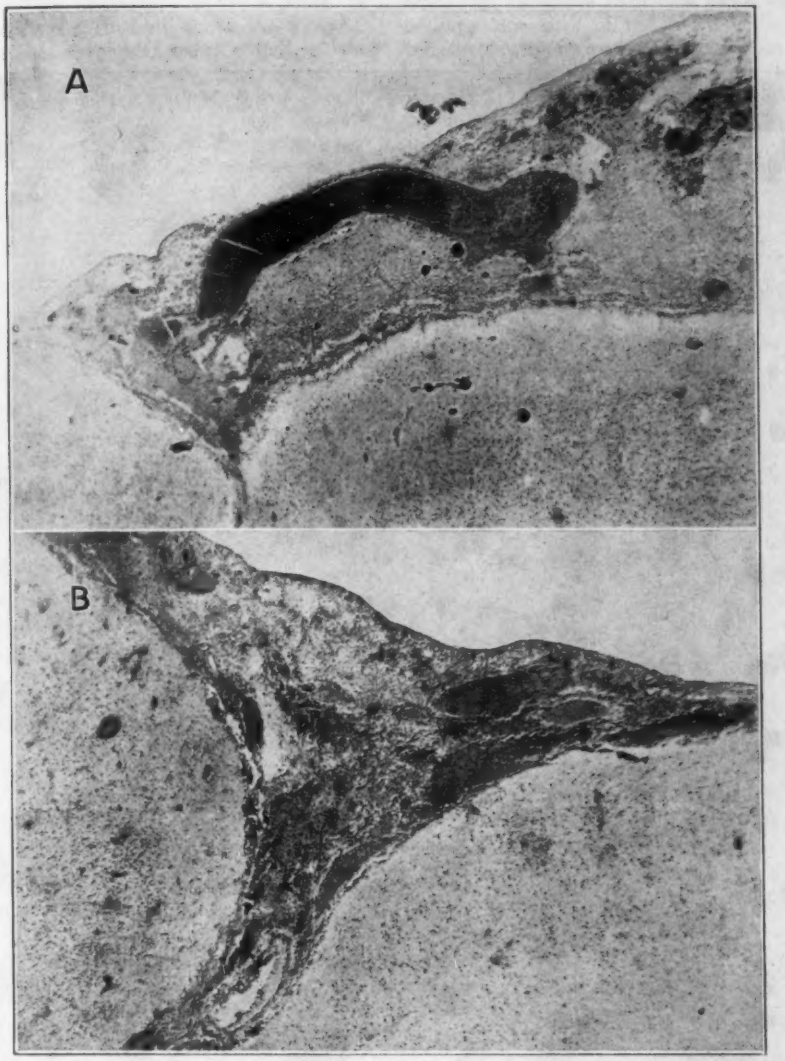


Fig. 11.—*A* and *B*, pronounced vascular congestion and hemorrhages in the meninges of the rabbit. Hematoxylin and eosin stain.

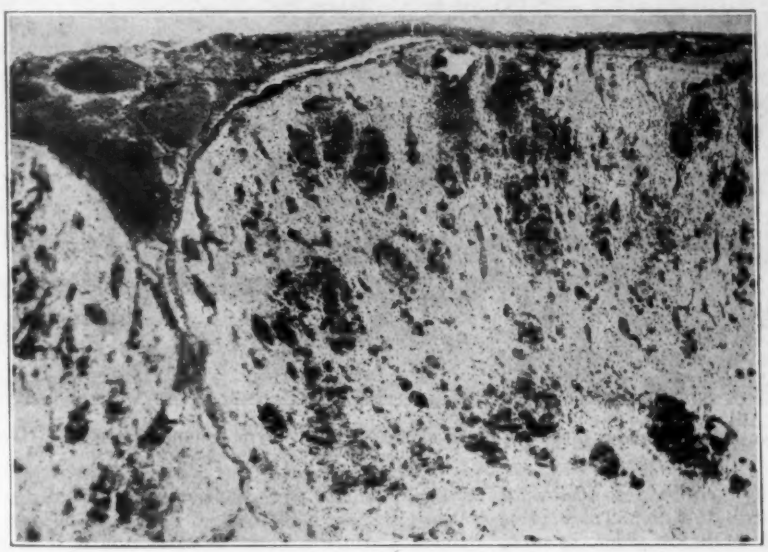


Fig. 12. Numerous hemorrhagic petechiae of the brain and parenchyma. Hematoxylin and eosin stain.

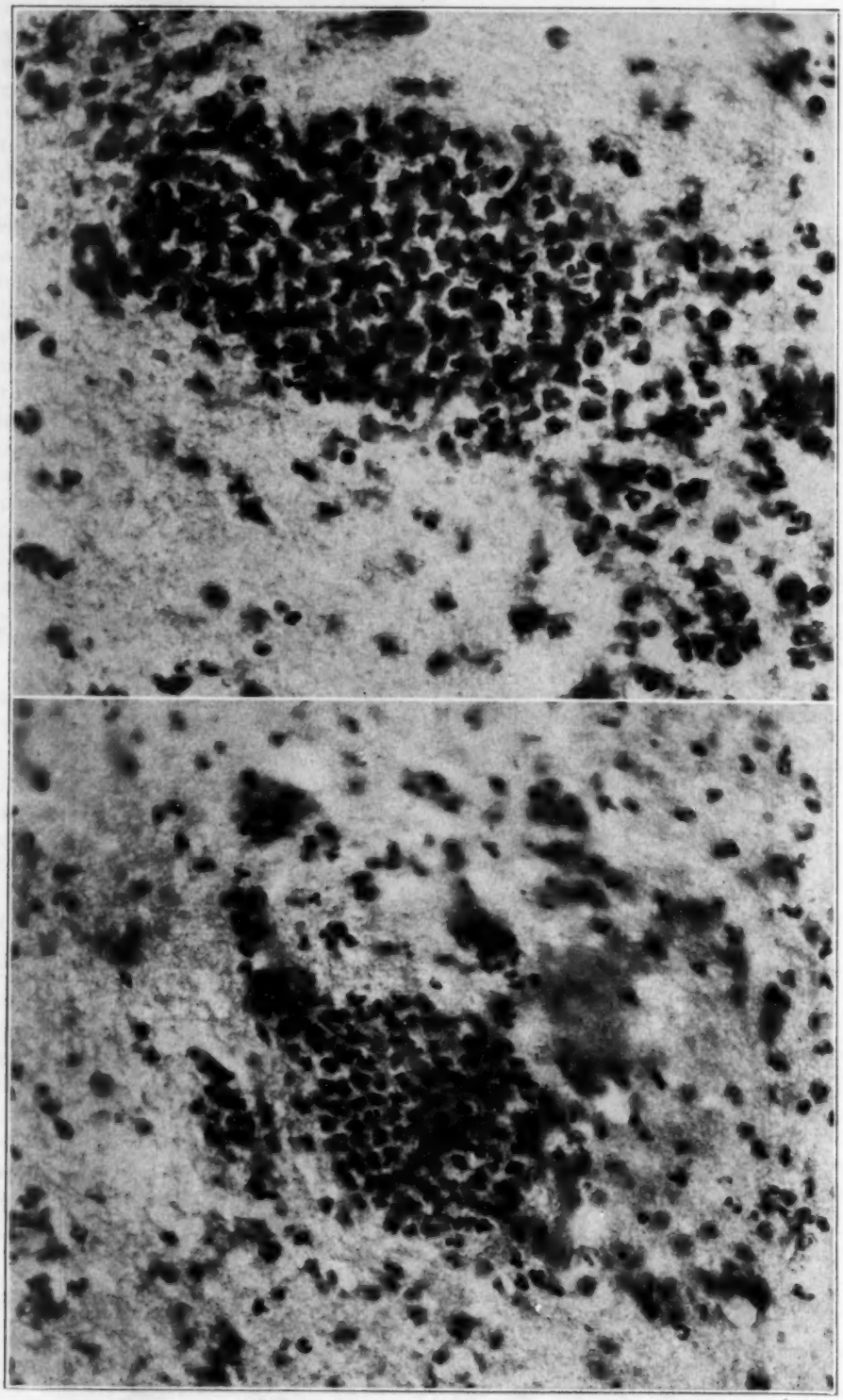


Fig. 13.—Perivascular exudate, formed almost exclusively of polymorphonuclear cells. Hematoxylin and eosin stain.

in the meninges. The dilatation of veins could be followed in the septums. In addition to the vascular engorgement, free hemorrhages were noted in the arachnoid covering (fig. 11), as well as in the subpial area. The red blood cells in the dilated blood vessels or in the free hemorrhages were at times individually outlined and well preserved; at other times homogenization of the cells was dominant. In the subpial areas one could recognize individual blood vessels surrounded by large numbers of red blood cells. The red blood cells generally formed a homogeneous mass, though it was not unusual to note either individual red cells or large collections of these cells still possessing a normal appearance. In the midst of the hemorrhages one often recognized pigment, probably of hematic origin, either free or included in phagocytic elements. The hemor-

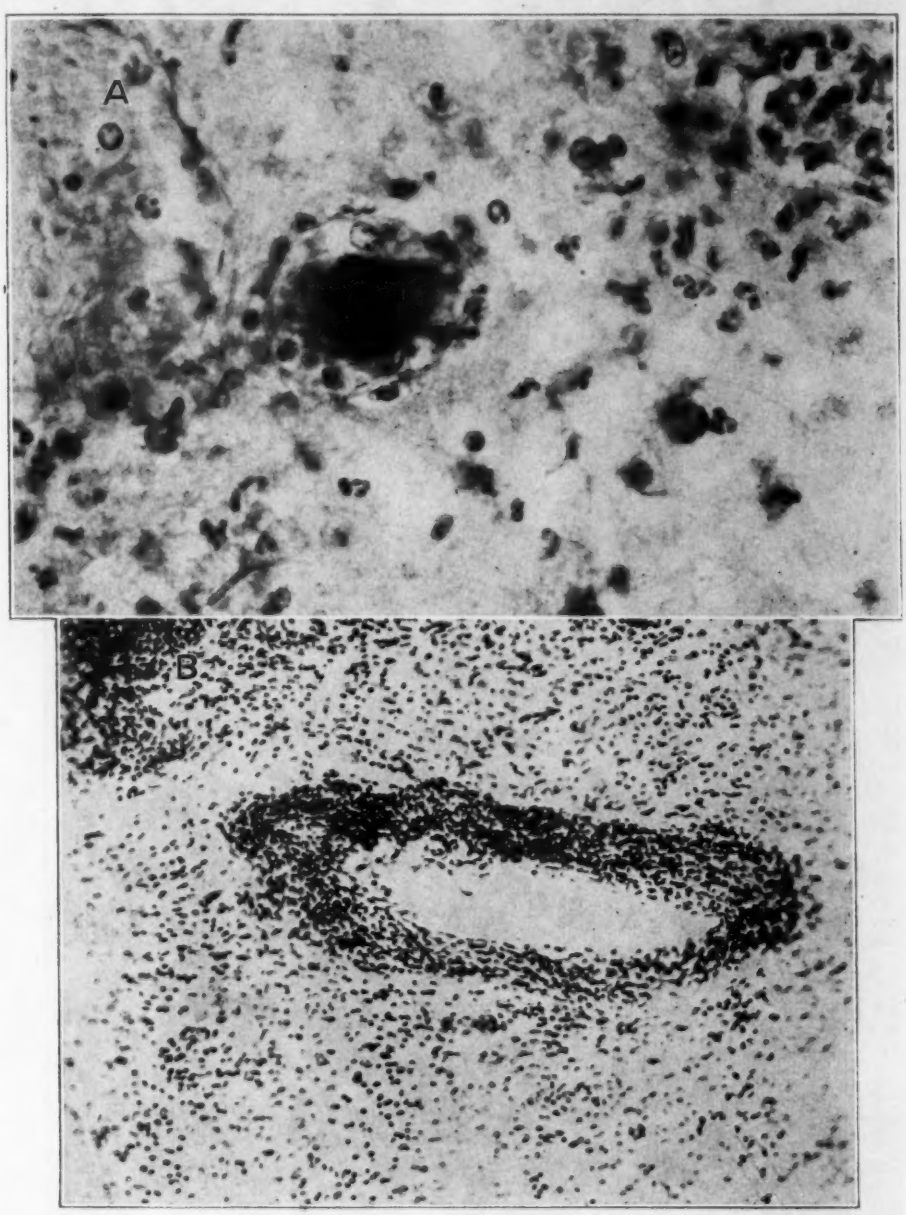


Fig. 14.—*A*, hyaline thrombus; hematoxylin and eosin stain. *B*, perivascular infiltration, formed predominantly lymphocytes; Nissl stain.

hemorrhages at places extended into the external layers of the cortex.

In the brain substance itself numerous petechial hemorrhages were noted, which in certain areas extended deep into the cortex, reaching the white matter (fig. 12). The petechial hemorrhages were chiefly about the blood vessels. Some of the petechiae were confluent, forming a large hemorrhagic mass, in which rhages were not diffuse but appeared concentrated in areas in the immediate vicinity of the injected antigen. Farther away there were no hemorrhages, although engorgement of blood vessels was a feature of wider distribution.

Next to hemorrhages, edema was conspicuous in the same areas of distribution. It was present either free in the tissue or more localized in the perivascular

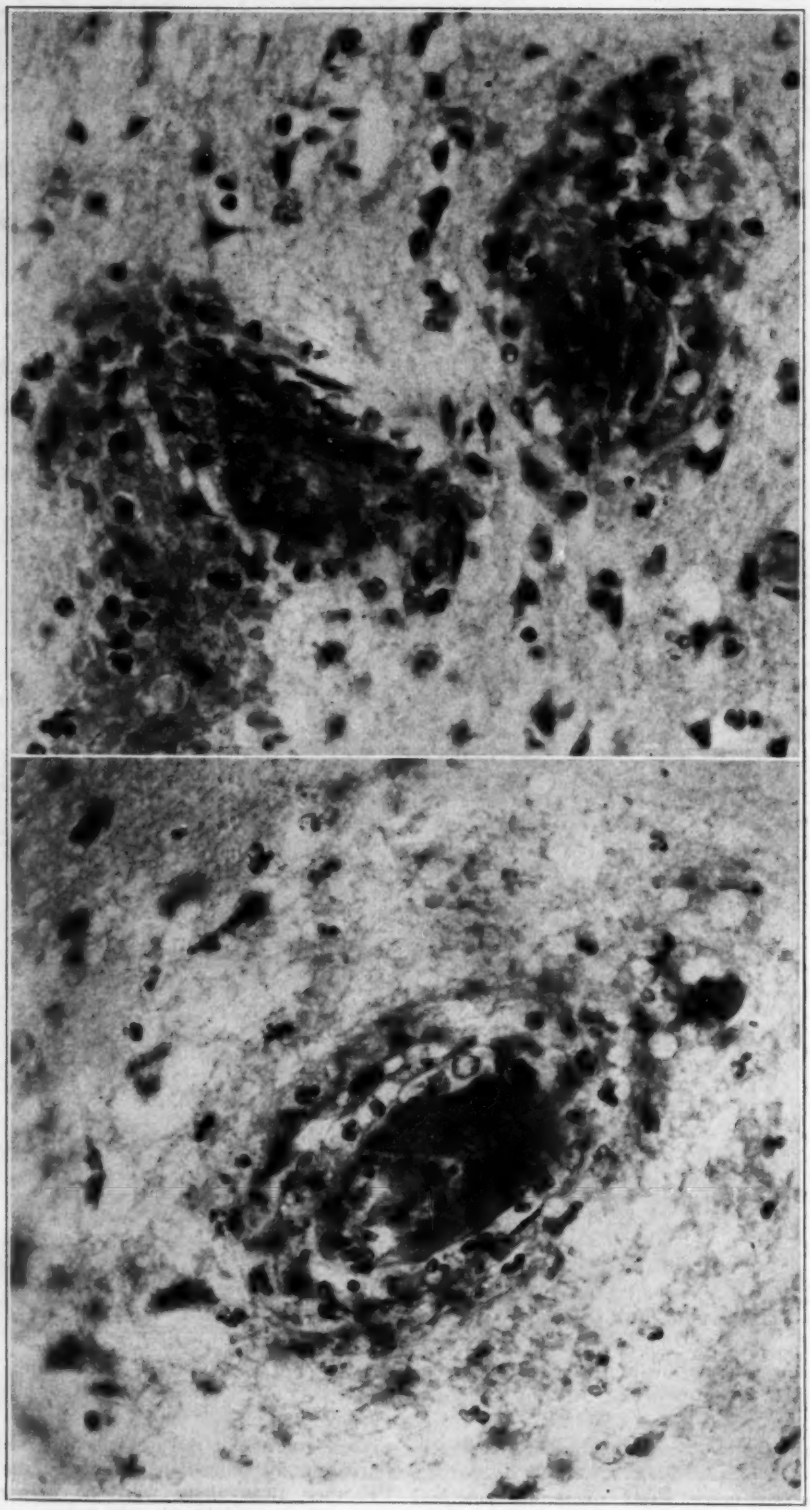


Fig. 15.—Thrombosed blood vessels surrounded by a few polymorphonuclear cells. Hematoxylin and eosin stain.

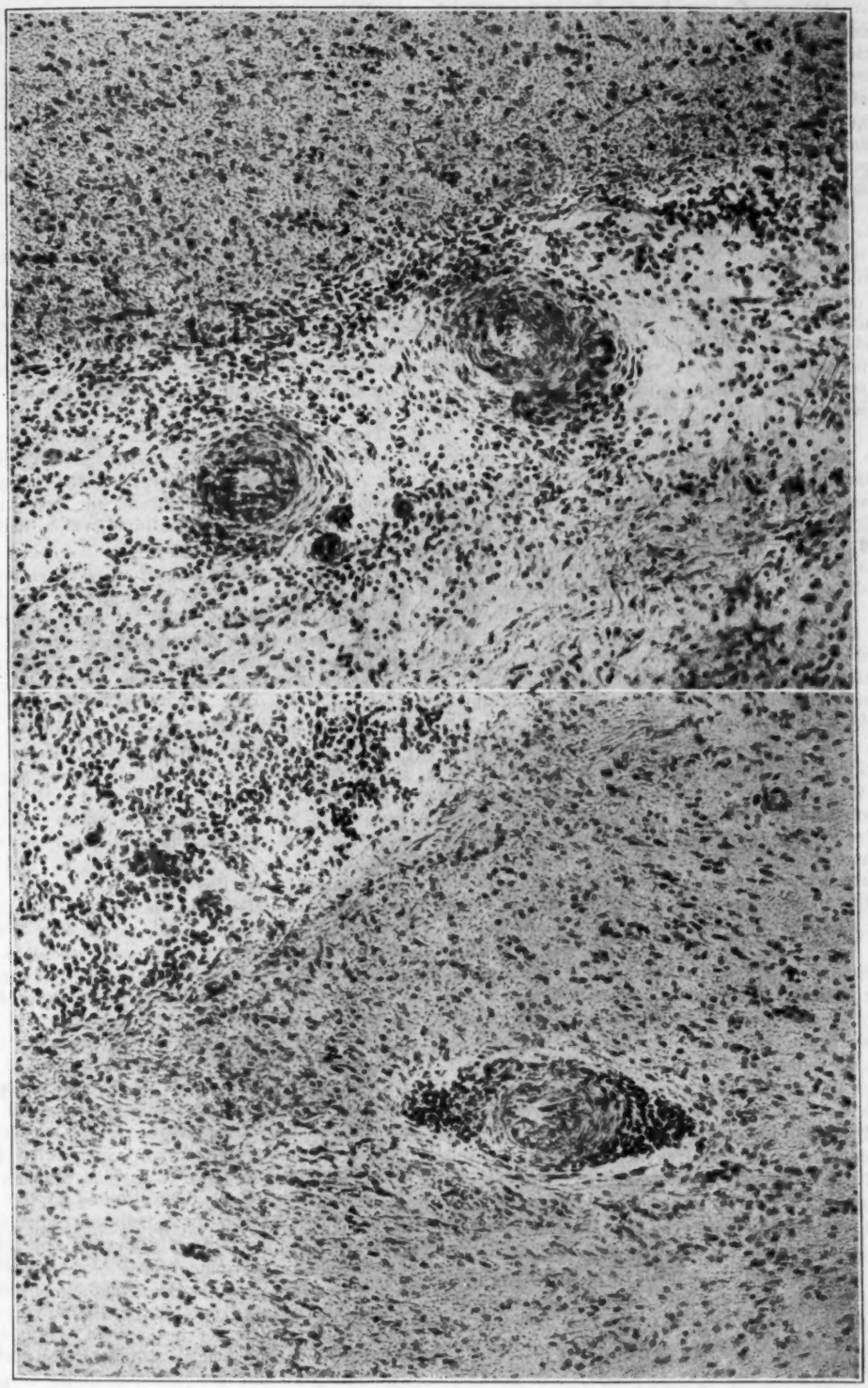


Fig. 16.—Progressive changes in the blood vessel walls, with marked proliferation of the intima. Hematoxylin and eosin stain.

spaces of His. At times it was more circumscribed in the Virchow-Robin spaces. The fluid had a homogeneous appearance and generally did not stain, though occasionally it was slightly blue. In the vicinity of the hemorrhages, the edema invaded the nerve parenchyma itself, and the perineuronal spaces were dilated. Acute swelling of oligodendrocytes contributed to the edematous appearance of the tissue.

In addition to hemorrhages and edema, the perivascular reaction constituted an outstanding feature. At this stage the exudate was formed almost exclusively of polymorphonuclear cells (fig. 13). The majority of the cells were neutrophils, and only occasionally were mast cells or eosinophils present. The leukocytes, collected around the blood vessels, were occasionally seen apparently free in the surrounding tissue.

Study of the blood vessel walls also revealed interesting facts. In some of the blood vessels subendothelial edema was evident. Other vessels disclosed homogenization of the walls, especially of the media, an expression of early degenerative change. No appreciable thickening of the adventitia was noted at that stage.

At this stage there was already, however, a tendency toward thrombus formation. This was expressed as an increase in the zone of plasma, which in certain cases occupied a good fourth or fifth of the lumen of the blood vessels, and as early pavementing of the leukocytes, the middle third of the stream being left free for the plasma zone and the central zone being occupied by red blood cells. Early thrombi, to which platelets and fibrin contributed, were seen here and there, and gradual hyalinization of the mass followed, with partial or complete occlusion of the lumen of the blood vessel (fig. 14 *A*). No appreciable organization of thrombi was detectable at this stage.

Monkey 14.—This animal received five intramuscular injections of 0.2 cc. of antigen (egg white) at two day intervals, followed in fifteen days by one intravenous injection of 10 cc. of the same antigen and, finally, fifteen days later by an intracerebral injection of 0.2 cc. of the same antigen. Death occurred six days after the intracerebral injection. During these six days the monkey had convulsions and displayed paretic symptoms on the side opposite that of the intracerebral injection.

The vascular reaction in this animal had undergone a striking change. The hemorrhagic features described in monkey 15 were present also in this animal; in addition, in the central, necrotic portion of the area of injection one could see that resorption of the red blood cells was taking place, as evidenced by homogeneous masses, in which none or few individual red cells were recognizable. The meninges did not disclose the pronounced congestion or the free hemorrhages noted in monkey 15 outside the site of injection. Perivascular hemorrhages were mild in extent and intensity as compared with the hemorrhages in the preceding animal.

At the periphery of the necrotic area the change in the type of perivascular exudate was more evident. Instead of the intense reaction, and almost exclusive presence, of polymorphonuclear leukocytes, lymphocytes and large mononuclear cells seemed to form the bulk of the exudate (fig. 14 *B*). Here and there among the lymphocytes a few polymorphonuclear cells could be seen. The perivascular cuffing of lymphocytes was more frequent about blood vessels in which definite thrombi were not present. When thrombi were present, they were mostly of the hyaline type, with no outstanding organization. About some of the thrombosed blood vessels occasional polymorphonuclear cells were present (fig. 15).

Progressive changes in the blood vessel walls had made their appearance at this stage. Definite thickening of the adventitia, with notable proliferation of the intima, leading to partial occlusion of the lumen, was noticeable (fig. 16).

In addition to lymphocytes, the presence of large mononuclear cells constituted one of the important variations in the perivascular exudate occurring at this stage. These large cells, presumably originating from blood elements or from the adventitia (adventitial cells or polyblasts), were present in increasing numbers as the chronicity of the reaction increased. A tendency for these cells to fuse together, especially in the adventitia, was already detected.

A notable histiocytic reaction had also made its appearance, and compound granular corpuscles were seen surrounding the lymphocytes or intermingled in the perivascular exudate. The compound granular corpuscles loaded with fat substances stained characteristically with scarlet R.

These vascular changes were noted not only in the immediate vicinity of the area of injection of the antigen but in remote portions of the central nervous system, such as the midbrain, the pons, the medulla oblongata and the cerebellum, which had no direct contact with the injected antigen.

Monkey 17.—This animal received eleven intracerebral injections of 0.2 cc. of antigen at weekly intervals, followed fifteen days later by eight additional intracerebral injections and, finally, fifteen days later, by an additional intracerebral injection. Thirty days later one intravenous injection of 10 cc. of antigen was administered, followed twenty-five days later by a final intravenous injection of the same antigen.

In this animal, for which the duration of the experiment lasted at least twenty-four weeks, the pathologic reaction had substantially changed. No hemorrhages were seen, and no polymorphonuclear leukocytes were noted in the perivascular exudate, where, instead, lymphocytes, large mononuclear cells and histiocytes predominated. At this stage the presence in the perivascular exudate of large polygonal cells of somewhat epithelioid appearance was outstanding. These cells, mixed with lymphocytes, showed a tendency to coalesce and form giant cells. The presence of these giant cells was also characteristic. They were noted in the perivascular exudate or, at times, within the walls of a blood vessel. They were present not only in the cerebral parenchyma but in the meninges (fig. 17).

Of importance at this stage was the presence of miliary granulomas in which typical giant cells were present. These granulomas were scattered in the various layers of the cortex, some being larger than others and histologically of various complex structures, the reaction being at times limited to the appearance of only one or two giant cells surrounding or occupying the lumen of the blood vessel (fig. 18).

Immediately surrounding the blood vessels, in addition to the large mononuclear, epithelioid-like and giant cells, were a large number of microglia cells, histiocytes of the central nervous system, which were undergoing proliferation and all stages of transformation, for the most part, into compound granular corpuscles.

Of interest was the fact that the reaction was not always of the same type, either in intensity or completeness. Sometimes the histiocytic reaction predominated; in other areas the granulomatous reaction, and in others the lymphocytic reaction was dominant, and the other components were less evident, or even absent. Thus,

in monkey 43, which received the antigen always by intracerebral injection except for the last injection, which was given intravenously, while the lymphocytic-histiocytic reaction was the dominant feature, no miliary granulomas were present, and only occasional giant cells were encountered.

Also, the presence of the pronounced histiocytic reaction, with formation of individual giant cells or small granulomas, was not limited to the areas of injections of the antigen but, as with the early stage of the reaction, was noted in distant regions, such as the medulla and the cerebellum, where no direct contact of the antigen with the tissue had been established.

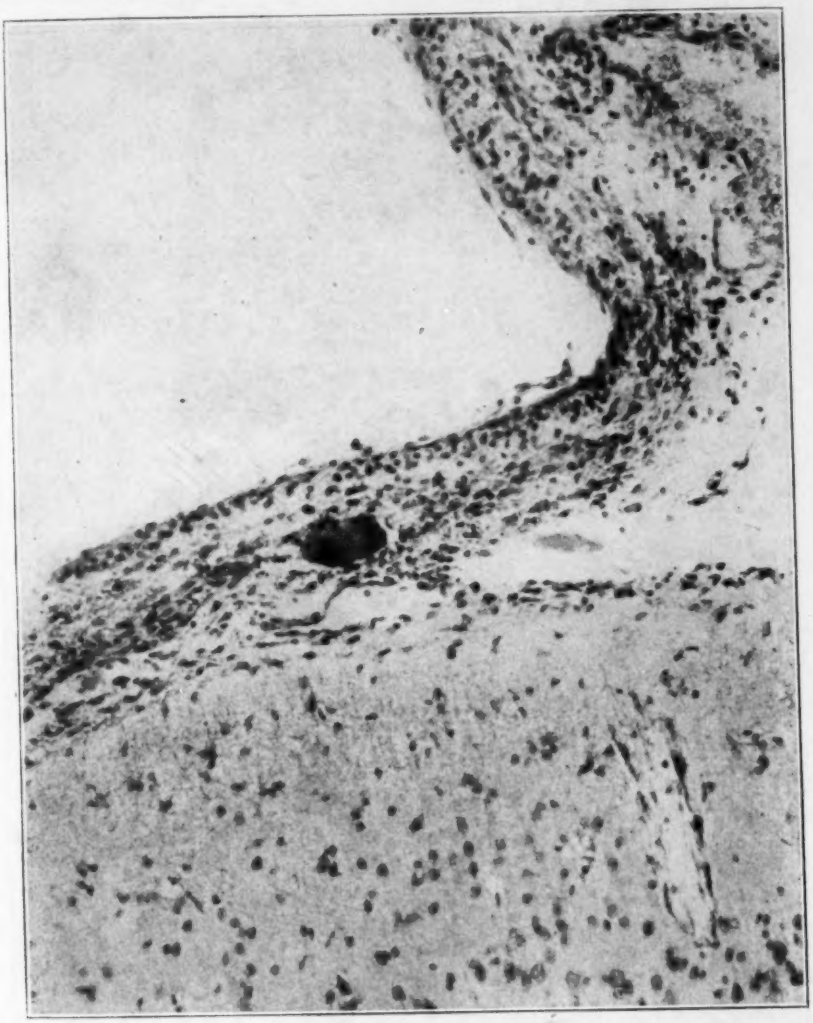


Fig. 17.—Large giant cell in the meninges. Hematoxylin and eosin stain.

Prior to this investigation, Jervis and I,[68] following the lead of experiments by Rivers, Sprunt and Berry [66] and Rivers and Schwentker,[67] had reported in 1940 on the cerebral pathologic changes following the intramuscular injection in monkeys of fresh aqueous emulsions and an alcohol-ether extract of normal rabbit brain.

In discussing the mechanism of production of the cerebral lesions, we stated [68]:

The hypothesis that antibodies specific for a given organ are responsible for certain diseases of unknown etiology has been brought forward many times, but little evidence has been produced that organ-specific antigens actually occur. However, as far as the central nervous system is concerned, recent experiments (Witebsky and Steinfeld; Schwentker and Rivers) have demonstrated that emulsions of heterologous brain tissue when repeatedly injected into rabbits are capable of inciting antibodies specific for the rabbit brain. The antibodies can be demonstrated either by complement fixation tests or by precipitin reactions. Further, brain-specific antibodies are also produced by an alcohol extract of brain provided an antigenically active protein is added. The reacting antigen appears to be a lipoid functioning as a haptene, which is actuated by a protein. It will be noted that in the present experiments a lipoid substance was contained in both the emulsion and the ether-alcohol extract, and a protein was doubtless present in the emulsion. There is, therefore, enough justification for assuming that the lesions in the brain may be associated with the development of antibodies specific for brain.

The 7 monkeys reported on in our study received from a minimum of twenty-nine injections to a maximum of one hundred and three injections, and the duration of the observation varied from a minimum of one hundred and twelve days to a maximum of four hundred and five days.

The pathologic changes in the brain were fundamentally similar with respect to the type of tissue reaction. The severity of the reaction varied from one animal to another but was not related to the number of the injections. Monkey 673, which received thirty-three injections in the space of one hundred and twenty-six days, presented as typical a pathologic picture as did monkey 696, which received one hundred and three injections in the course of four hundred and five days.

An outstanding feature of the process refers to the absence of any pathologic change referable to the acute "Arthus phenomenon." No hemorrhages were noted in the meninges or in the parenchyma of the brain, either in the form of perivascular petechiae or free in the tissues. Neither was the exudate formed predominantly of polymorphonuclear cells. We noted no stage of the perivascular reaction comparable to the early stages of the reaction following intracerebral injections of antigen.

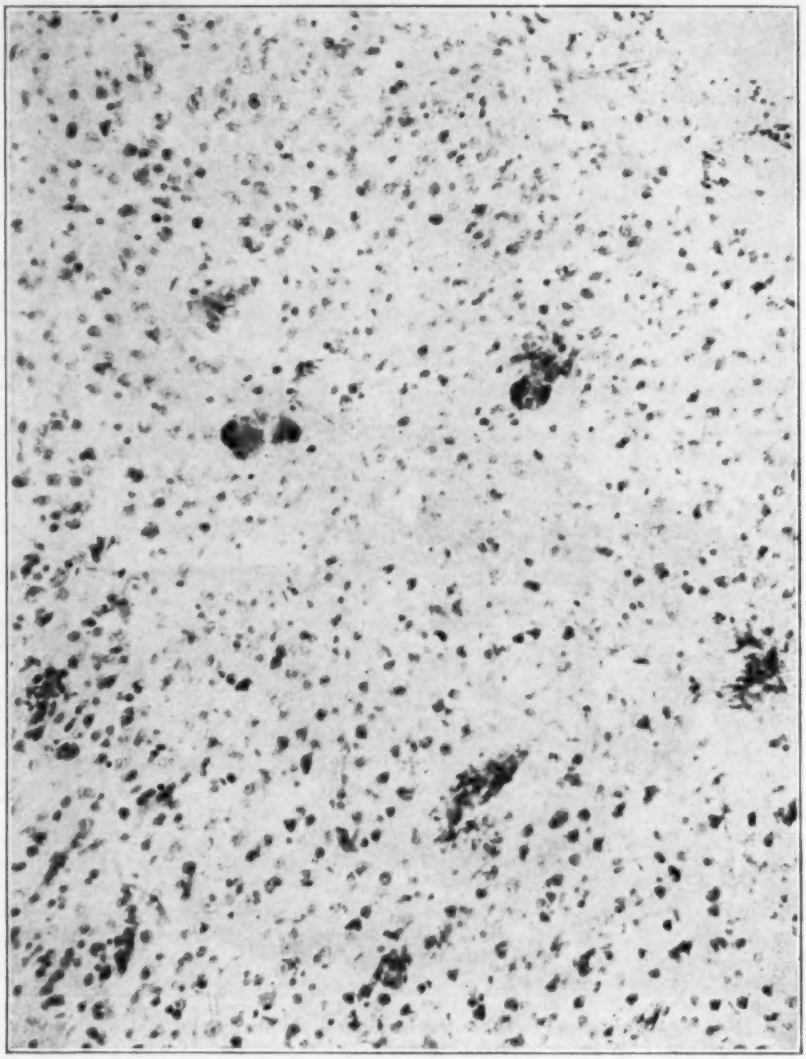


Fig. 18.—Giant cells surrounding blood vessels in the cerebral cortex. Hematoxylin and eosin stain.

The perivascular reaction was fundamentally one of lymphocytes and histiocytes and could be classified under three main types: In the first type the cellular reaction consisted mainly of compound granular corpuscles. In the second type, the infiltration consisted mainly of lymphocytes; here and there, in certain areas, poly-

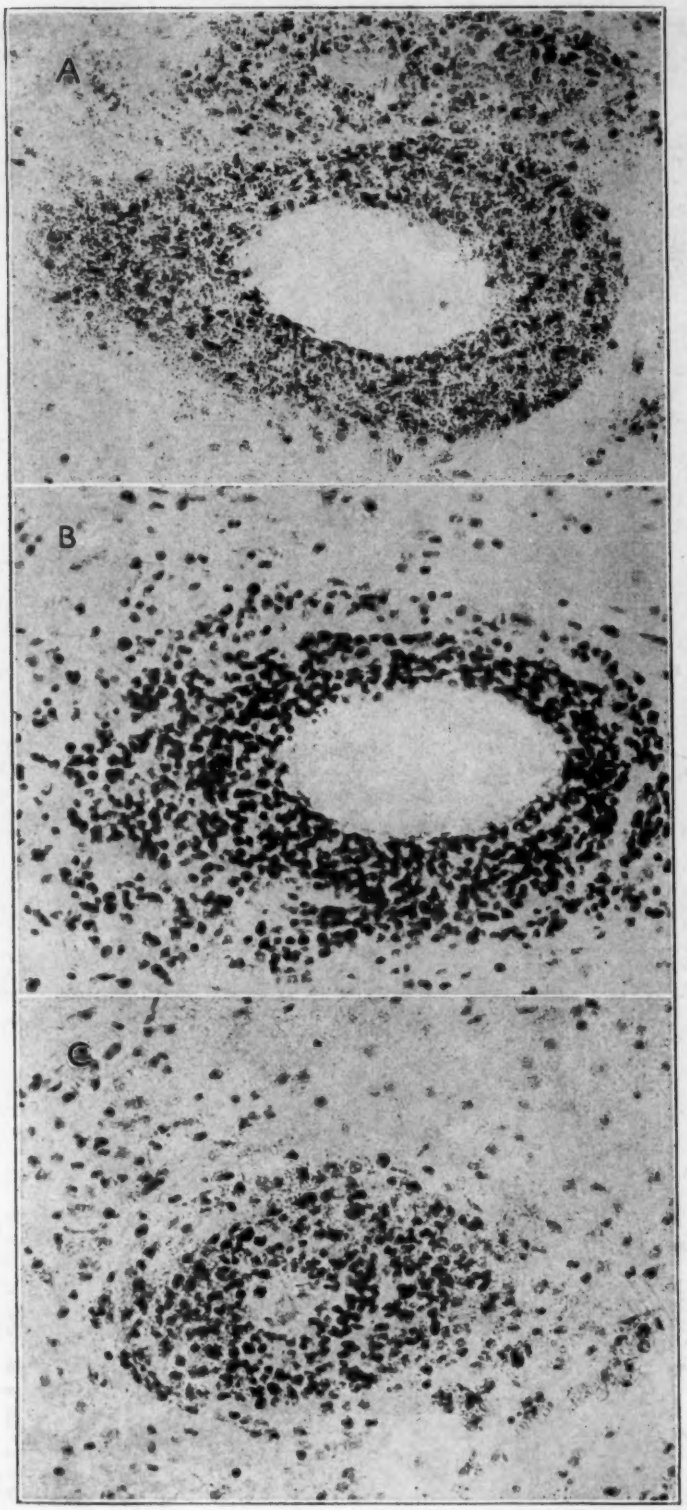


Fig. 19.—Various types of perivascular reactions. *A*, compound granular corpuscles; *B*, lymphocytes; *C*, mixture of the two types of cells. Nissl stain.

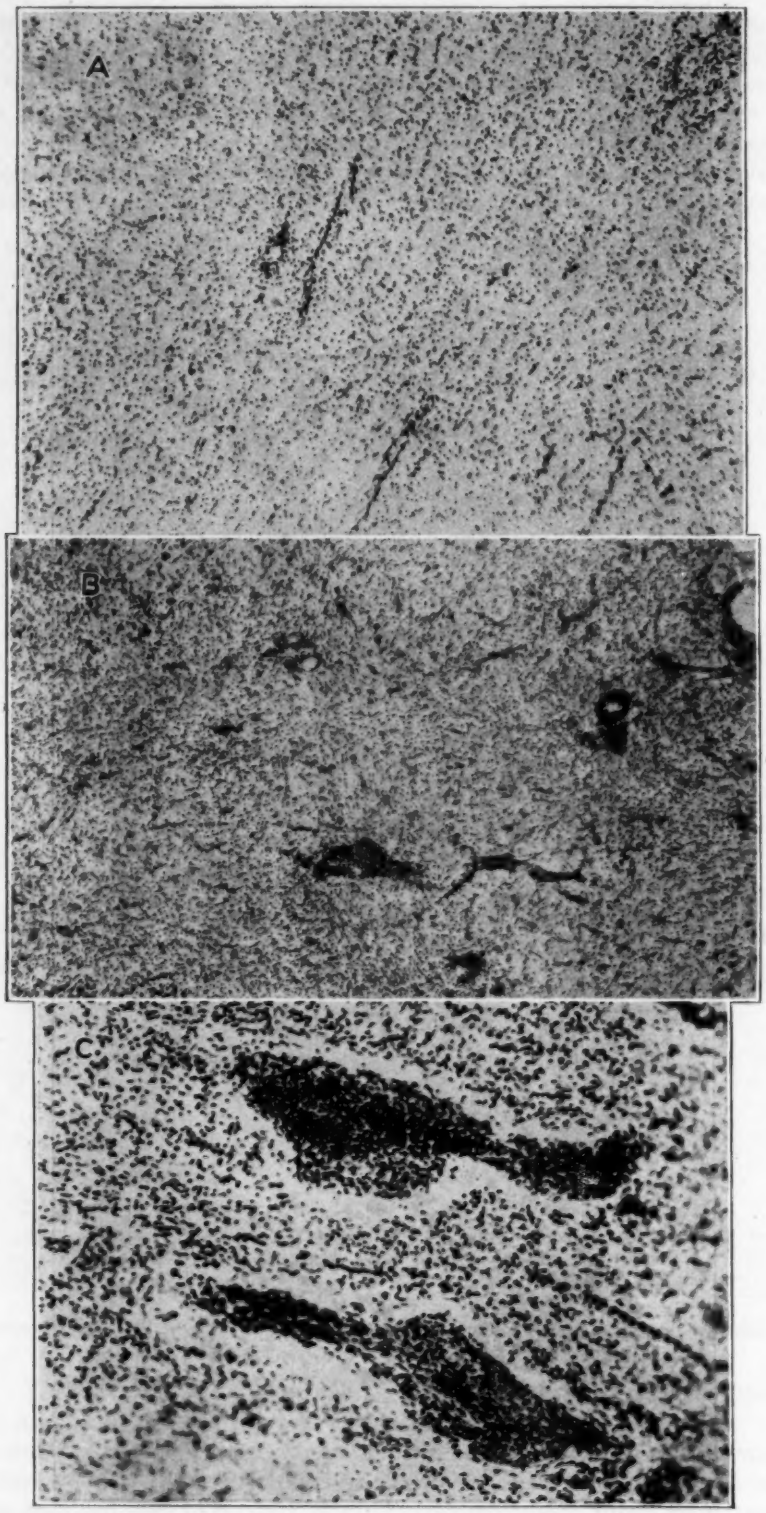


Fig. 20.—Three degrees of intensity of the perivascular reaction. *A*, very mild; *B*, moderate, and *C*, pronounced. Nissl stain.

morphonuclear and plasma cells were seen. In the third type, both hematogenous elements and histiocytes — compound granular corpuscles — were present, with the compound granular corpuscles generally distributed at the periphery and tion and early organization were encountered. Finally, the development of some of the small blood vessels were occluded as a result of granulomatous formations in the blood vessel walls themselves especially in the intima.

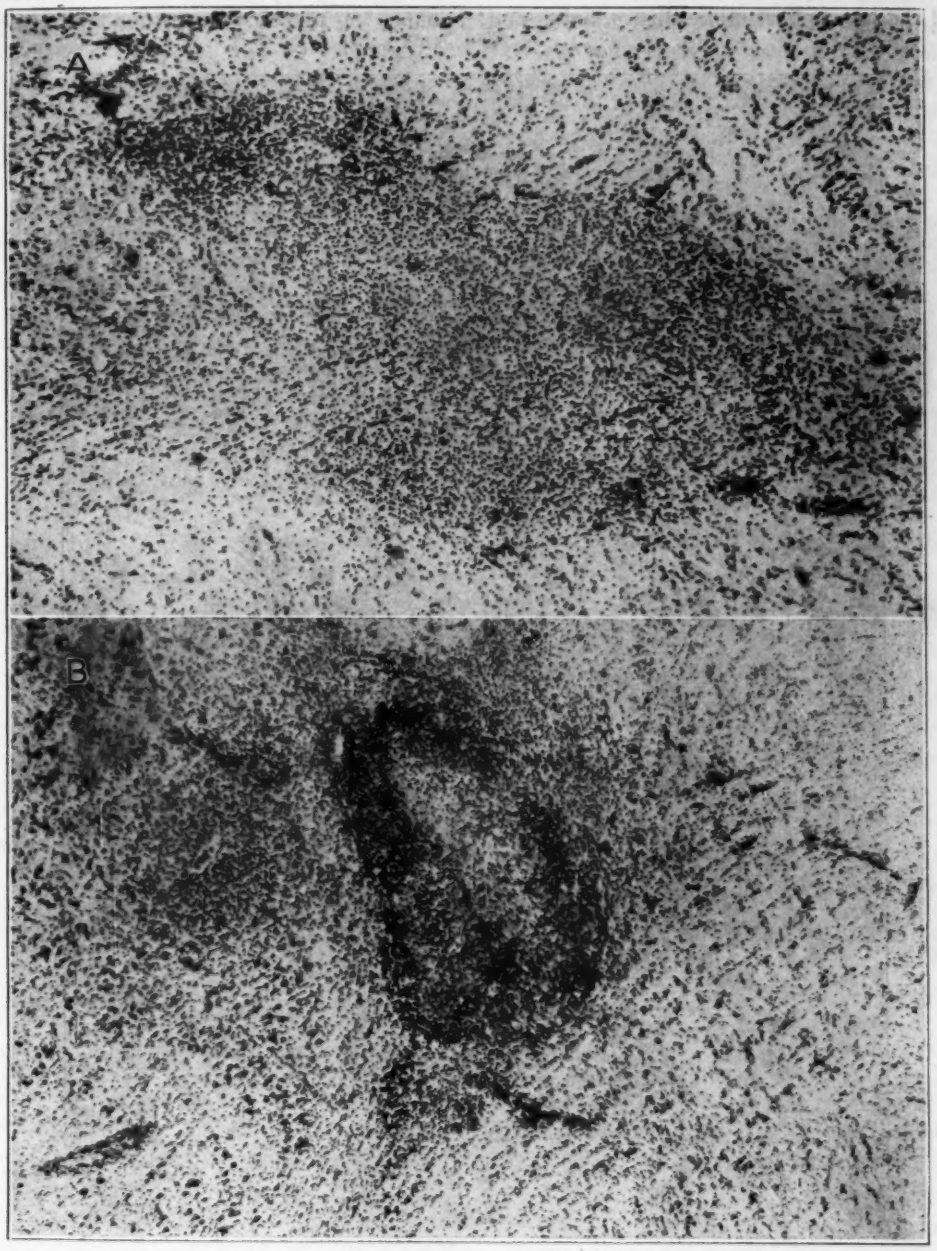


Fig. 21.—Early (*A*) and advanced (*B*) stages of necrosis. Nissl stain.

the lymphocytes occupying the central portion of the mass of exudate (fig. 19).

A second study of the slides revealed degeneration of blood vessel walls, especially hyalinization and thickening of the adventitia. Thrombi were at times represented by plugs of degenerated red blood cells. In some of the thrombi fibrin forma-

All gradations in the intensity of the perivascular reaction could be seen from very mild to intense. Figure 20 illustrates the occurrence of a mild, a moderate and a pronounced perivascular reaction. The intensity of the parenchymal damage also varied from one area to another.

Figure 21 illustrates two stages of necrosis. In the necrotic area, in addition to fragments of nerve elements, compound granular corpuscles were noted in considerable numbers. The pathologic changes were widely distributed throughout the brain but were most frequent in the white matter of the hemisphere. The diencephalon and large mononuclear cells were present in the exudate and gave the impression of originating from the cellular elements of the adventitia. A large number of these cells were polynucleated and constituted characteristic giant cells of the foreign body type; these giant cells were numerous and in places were an outstanding feature of

Fig. 22.—Numerous giant cells in the midst of a perivascular reaction. Nissl stain.

the mesencephalon were also distinctly involved. The major intensity of the pathologic process occurred, however, in the pons, the medulla oblongata and the cerebellum.

Not only lymphocytes or a combination of lymphocytes and compound granular corpuscles was noted about the blood vessels, but often the histologic process (fig. 22). In addition to their apparent origin from large mononuclear cells or from cells of the adventitia, their origin from the histiocytes of the region (microglia cells) could not be excluded. The impression was received that in some cases fusion of histiocytes resulted in giant elements.

There seemed to be no relation between the giant cells and the severity of the damage to the tissue, inasmuch as giant cells were present not only in regions of severe involvement but in areas where only small foci of vascular reaction were noted. At times the intensity of the reaction dominated by giant cells was such as to give the impression of a tumor-like structure (fig. 23). The analogy between figures 7 *A* and *B*, reproduced from Scherer,[101] and figure 23 throws light on the difficulty of interpreting certain pathologic reactions if one does not take into account the pathologic character of allergic reactions.

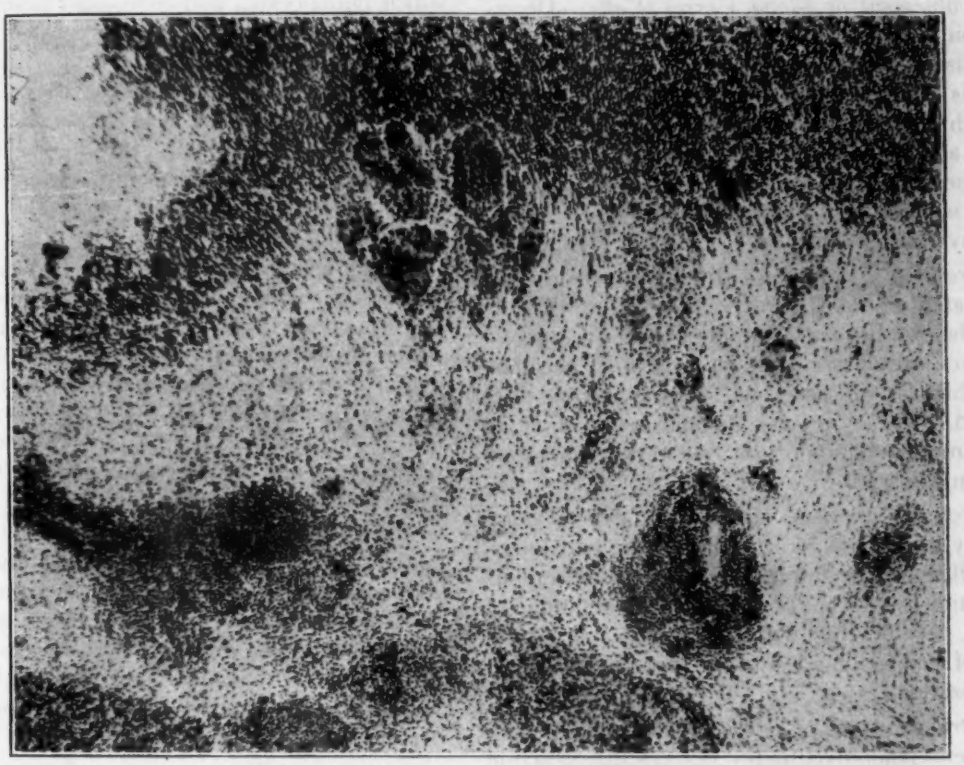


Fig. 23.—Severe perivascular reaction. In the upper part of the picture is a nodule formation, with numerous giant cells reminiscent of tumor structure. Nissl stain.

The reactions following a protracted course of intramuscular injections of brain emulsion in the monkey differ from the reactions of the acute stage of experimental cerebral anaphylaxis (Arthus phenomenon) but resemble more closely the responses observed in its advanced stages. In this connection the sensitization of the animals receiving the protracted course of injections required from a minimum of one hundred and twelve days to a maximum of four hundred and five days.

The time factor and the factor of gradual, protracted sensitization must play an important part in the variation of the histologic picture, for in these experiments hemorrhages were absent, whereas hyperemia, thickening of blood vessel walls and thrombosis were still observable. On the other hand, the perivascular type of reaction was fundamentally of monocytic-histiocytic type. Indeed, my observations indicate that lymphocytes, large mononuclear cells and histiocytes form the bulk of the perivascular reaction. Here, as in the later stages of direct cerebral anaphylaxis, characteristic giant cells were also associated with a pronounced histiocytic reaction (microglia reaction). The meninges, also, though to a much less pronounced degree, disclosed the presence of perivascular reaction and involvement of the blood vessel walls, similar to the response in the nerve parenchyma.

PATHOLOGIC CHARACTER OF EXPERIMENTAL CEREBRAL ANAPHYLAXIS AS COMPARED WITH THAT OF DEMYELINATING DISEASE

Demyelination.—In acute disseminated encephalomyelitis, acute disseminated sclerosis and multiple and diffuse sclerosis the demyelination is chiefly perivascular. In experimental cerebral anaphylaxis demyelination is noted particularly around blood vessels.

Hemorrhages.—In cases of acute multiple sclerosis and acute disseminated encephalomyelitis hemorrhages of various distribution have been reported. Hemorrhages, both large and small, are an important feature of the acute stage, or Arthus phenomenon, of experimental general or cerebral anaphylaxis.

The paucity in general of hemorrhages in the chronic stages of disseminated or diffuse sclerosis has its parallel in the gradual disappearance of hemorrhages in the more advanced stages of experimental cerebral anaphylaxis.

Involvement of Blood Vessel Walls.—Degeneration (homogenization, hyalinization, arteriofibrosis and thickening) of the walls of blood vessels has been reported in cases of both acute and chronic disseminated sclerosis, diffuse sclerosis and acute disseminated encephalomyelitis. Degeneration and necrosis of the blood vessel walls is a common feature of acute experimental anaphylaxis.

Thrombus Formation.—In cases of acute disseminated sclerosis, diffuse sclerosis and acute encephalomyelitides Putnam [103] and his coworkers demonstrated the presence of thrombi, for which at times special staining methods are needed. These venous thrombi, according to Putnam, play an important role in the production of demyelination.

Thrombi are associated with experimental anaphylaxis of the skin, joints, heart and lungs, as well as of the brain. All stages of thrombus formation may be observed, accumulation of fibrin, pavementing with leukocytes and formation of red cell and hyaline thrombi to actual organization.

Distribution of Perivascular Reaction.—In acute encephalomyelitis the perivascular reaction is often predominantly perivenous. In multiple sclerosis, especially the acute type, the perivascular reaction is also predominant about the veins, though later it involves the capillaries and arteries.

In experimental cerebral anaphylaxis, as well as in anaphylaxis of other organs, investigators have emphasized the predominance of perivenous reaction.

Type and Intensity of Perivascular Infiltration.—In cases of acute and chronic disseminated sclerosis, acute and chronic diffuse sclerosis and acute encephalomyelitis perivascular infiltration, in various degrees, at times prominent, is almost always present. It is true that in some cases of chronic multiple sclerosis the perivascular reaction is minimal, but one must consider that the chronic type has run a course of many years and that the original pathologic picture has presumably undergone extensive modifications. The cellular elements which compose the exudate in these demyelinating diseases are mostly lymphocytes and compound granular corpuscles, arranged in parallel rows or intermingled. Microglia cells, the histiocytes of the brain, are numerous about the areas of the exudate or are mingled with it. The presence of large mononuclear cells and epithelioid elements has also been frequently reported.

The same consistent perivascular reaction, in which lymphocytes and compound granular corpuscles predominate, has been reported with experimental anaphylaxis of the brain. In anaphylactic reactions of other organs the same perivascular reaction has been consistently noted. Large mononuclear cells and histiocytes have been reported rather constantly in cases of the advanced stages of both general and cerebral experimental anaphylaxis.

The absence or scarcity of polymorphonuclear cells in the exudate of acute demyelinating processes in the chronic stages of the process is similar to such cells in the later stages of experimental anaphylaxis. In the early stages of the reaction the exudate is formed by polymorphonuclear cells, but in the subsequent stages lymphocytes and histiocytes constitute the bulk of the cellular infiltration.

Since most of the cases of the acute demyelinating processes have been studied pathologically several days to several months after the clinical onset, and cases of the more chronic stages of disseminated and diffuse sclerosis years after the onset, it is not surprising that the lymphocytic-histiocytic type of cellular reaction dominates the picture.

Giant Cells.—The occurrence of giant cells in cases of acute disseminated encephalomyelitis or acute multiple sclerosis, as reported by various authors, constituted a feature the significance of which was obscure. This is reflected in the effort of certain investigators, such as Scherer [101] and de Lange,[102] to explain their presence in demyelinating disease on the basis of an association of a neoplastic process with multiple or diffuse sclerosis or on the basis of transitional stages between the two processes.

Now, with knowledge of the pathologic process of experimental anaphylaxis, in which the presence of giant cells and granulomatous formation is explained as an allergic reaction, one can more easily see the link between the human and the pathologic process in man and the changes induced experimentally, and is in a better position to consider the presence of giant

cells and granulomatous reaction as an integral, though not a constant, feature of the pathologic process of demyelinating diseases.

Necrosis.—Areas of necrosis have often been reported in cases of acute multiple sclerosis and acute disseminated encephalomyelitis, as well as in cases of multiple and diffuse sclerosis. Necroses, on the other hand, are a frequent feature of experimental anaphylaxis.

one should evaluate the prominent gliosis of the chronic stages in the light of the generally long duration of the disease.

In the later stages of the anaphylactic lesion in the skin, joints or other organs, neoformation of mesodermic tissue, leading to a cicatricial process, has been reported. Jervis and I reported the occurrence of patchy gliosis with experimental cerebral anaphylaxis.

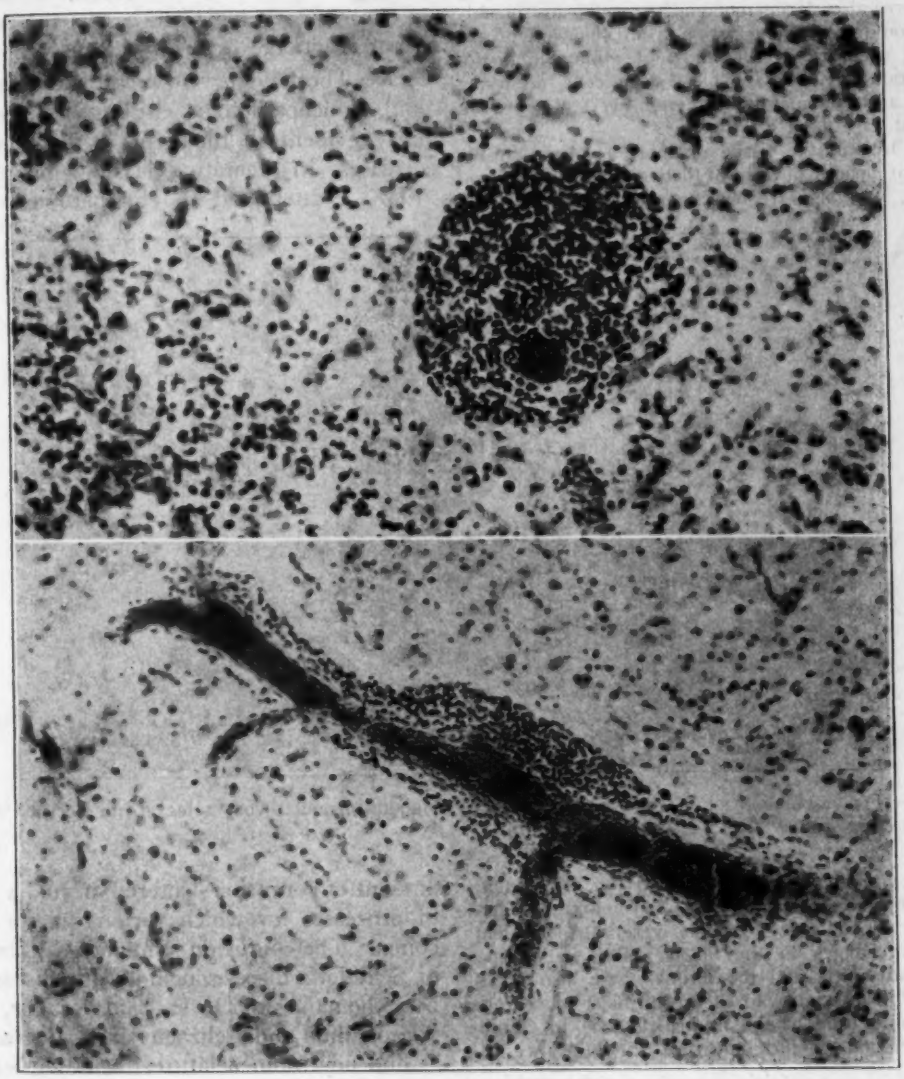


Fig. 24.—Cross and longitudinal section of blood vessels surrounded by a multilayered exudate of lymphocytes (from Ferraro[75]). Hematoxylin and eosin stain.

Repair.—Gliosis in the nervous system is in part the equivalent of the cicatricial process of repair in other organs. The patchy or diffuse gliosis (sclerosis) characteristic of the demyelinating process is generally viewed as the equivalent of such repair. One cannot expect to encounter pronounced or extensive gliosis in the acute stages of the demyelinating process, and

The similarity of the pathologic changes associated with acute and chronic demyelinating diseases and the pathologic features of experimental anaphylaxis of the brain establishes, in my opinion, a definite analogy between the two processes.

Encephalitis Complicating Scarlet Fever.—I[75] had the opportunity of comparing the aforementioned pathologic characteristics of

anaphylactic reaction in the brain tissue with the histopathologic changes in the brain in 2 cases of postscarlatinal encephalitis.

In the 2 cases there was wide distribution of demyelination and perivascular reaction. The cellular elements surrounding the blood vessels were mostly lymphocytes and histiocytes. The intensity of the cellular reaction varied from one area to another, although often multilayered cuffing of lymphocytes was noticeable (fig. 24). Also, blood vessels were seen surrounded predominantly by compound granular corpuscles (fig. 25). There, also, large mononuclear cells, presumably arising from blood elements or from elements of the adventitia, occurred in the midst of a notable histiocytic reaction (fig. 26). Typical giant cells, occurring as part of a granulomatous formation, were also present in the first case (fig. 8 *B*).

Edema, free in the tissue or more localized in the perivascular spaces of His or between the intima and the media, was also frequently encountered (fig. 27).

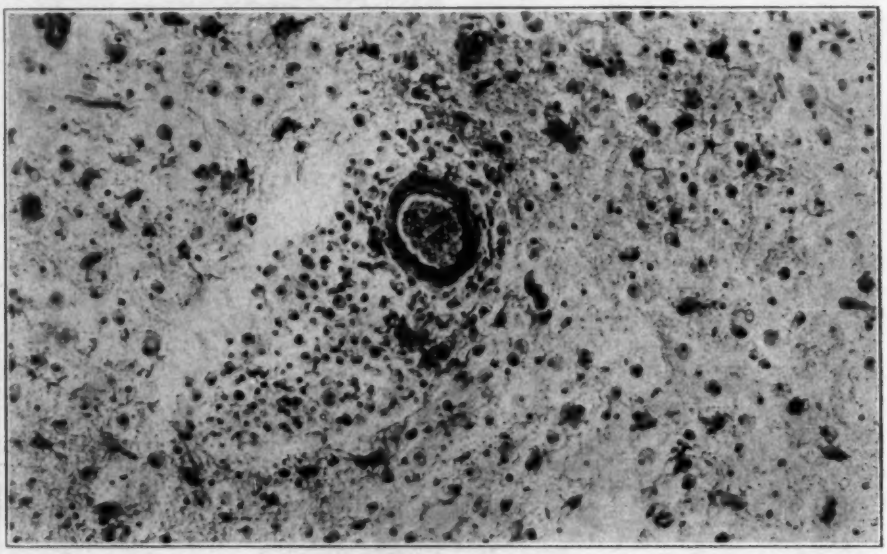


Fig. 25.—Perivascular reaction consisting chiefly of compound granular corpuscles (from Ferraro[75]). Hematoxylin and eosin stain.

Necrosis was an important feature (fig. 28). Hemorrhages were occasionally noted. Thrombi and degeneration of blood vessel walls were also present. Progressive changes in the blood vessel walls especially the adventitia and the intima, were also noted, particularly in proximity to or in the midst of necrotic areas. Proliferation of the intima resulted in considerable restriction of the lumen of the blood vessels (fig. 29).

On the basis of the analogy of these changes with the pathologic alterations of experimental anaphylaxis of the brain, I expressed the opinion that the pathologic process of postscarlatinal encephalitis could be viewed in the light of an allergic reaction.[75]

COMMENT

Up to the present the difficulty in the evaluation of the pathologic process of demyelinating diseases has centered, in my opinion, around four factors: (1) a tendency on the part of investigators to create easily new clinical or pathologic entities; (2) lack of discrimination between chronic and acute pathologic changes; (3) individual tendencies to be dogmatic in interpretation of the vascular reaction and labeling of the pathologic process as inflammatory or degenerative, and (4) lack of experimental support for the establishment of a link between an acute and a chronic pathologic process on the basis of vascular reaction.

1. The tendency to create easily new clinical and clinicopathologic entities has been particularly evident in the field of the demyelinating diseases. In a tentative classification, published in 1937, I attempted to eliminate a considerable amount of confusion centered around a multitude of processes for which various names had been coined. The confusion stimulated by the creation of Schilder's disease included the diseases which bear the names of Devic, Balò, Krabbe, Foix and Alajouanine and Pelizaeus and Merzbacher.

The new nomenclature, including such terms as centrolobar sclerosis, encephaloleukopathia scleroticans, leukodystrophy, degenerative subcortical encephalopathy, leukoencephalopathy myeloclastica primitiva and encephalomyelomalacia chronica diffusa, added confusion to a point at which neither the clinician nor the neuropathologist could see his way clear.

Minimal clinical or pathologic deviations cannot, in my estimation, constitute grounds for the creation of new clinicopathologic entities when one takes into consideration the variations

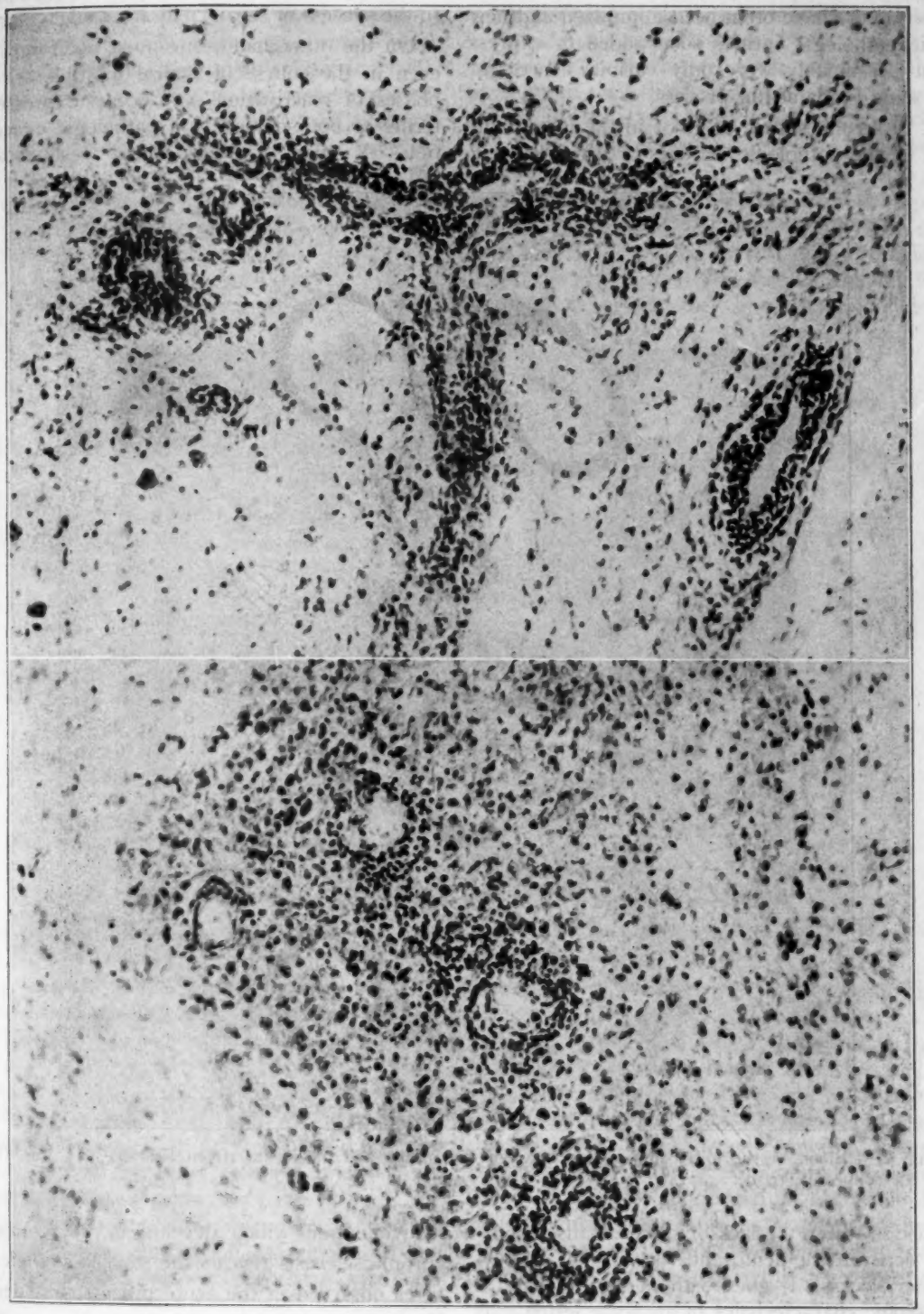


Fig. 26.—Pronounced perivascular reaction, in the midst of which large mononuclear and binucleated cells are present (from Ferraro [75]). Nissl stain.

related to the acuteness or chronicity of the process, the age of the patient and the individual resistance of the nerve tissues. Unfortunately, these factors have often been minimized and new clinicopathologic entities soon added to express what presumably were only various aspects of the same fundamental process.

2. A second source of error in the interpretation of the pathologic features of demyelinating disease has been the lack of sufficient discrimination between the acute and the chronic changes of the process. It goes without saying that the pathologic characteristics of an acute lesion may not be the same as those of the chronic lesion. Too often the difference in the pathologic features supposedly existing between an acute and a chronic demyelinating process is based on disregard of the fact that in the acute stage of demyelinating disease the process is in its development, whereas in the chronic stage important transformations of some reactions, in addition to the process of repair, may have taken place.

On the other hand, one must not forget that even in the course of typical multiple sclerosis phases of reactivation may occur, expressed in terms of both clinical and pathologic exacerbation. A study of the so-called fresh areas of demyelination which develop in the course of chronic sclerosis reveals the same histologic features observed in the acute processes of demyelination, ranging from pathologic changes of the blood vessel walls and perivascular exudate, in which both lymphocytes and compound granular corpuscles are represented, to thrombi, hemorrhages and necrosis.

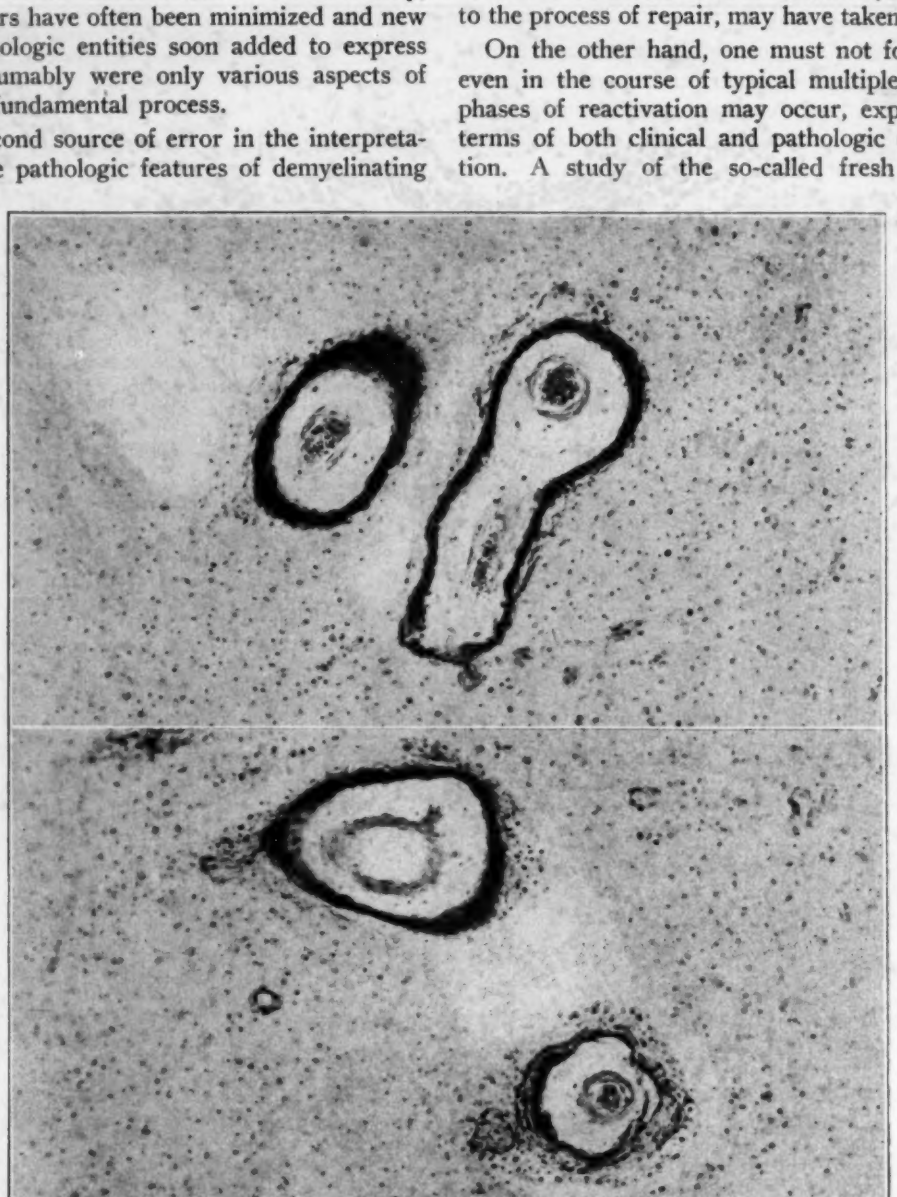


Fig. 27.—Blood vessels disclosing edema between the intima and the media (from Ferraro[75]). Van Gieson stain for connective tissue.

3. The third point of controversy relates to the interpretation of a pathologic process as inflammatory or degenerative. Here, again, the individual variations determined by the intensity and the duration of the pathologic process must be considered. Variations in connection with the intensity of the process are to be expected. In cases of dementia paralytica with classic symptoms microscopic examination has revealed considerable variation in the intensity of the perivascular infiltration, the amount of exudate being enormous in some cases and only moderate in others. Degenerative changes have been proved to predominate over the inflammatory changes in the juvenile form of dementia paralytica, whereas perivascular infiltration predominates in the so-called fulminating form.

With demyelinating processes, also, one should not be surprised to find cases in which the perivascular infiltration is outstanding and others in which this feature is much less pronounced. Evidently, the question may concern the degree of intensity of the same reaction, and not different pathologic processes.

To label a process as degenerative just because the perivascular infiltration is minimal means one's losing track of the process as a whole and disregarding the important possibility that mild reactions may be dependent on the intensity of the pathologic process and on the individual tissue resistance. In addition, the age of the process must play a part in the histologic appearance of the lesion. The paucity of perivascular reaction in the so-called chronic stage of epidemic encephalitis is familiar to all.

One solution of the difficulty in interpretation of the presence of perivascular exudate has been to include this reaction under "symptomatic inflammation." In this term the various authors have found an escape from, rather than an explanation for, the presence of a perivascular reaction associated with a lesion of supposedly degenerative nature.

How intense this symptomatic type of perivascular reaction should be to qualify for such a label has been left entirely to the individual investigator, no satisfactory standard having been set. Thus, study of the same histologic slide by two different pathologists might result in the diagnosis of the same process as inflammatory by one and as degenerative by the other. On the other hand, one must keep in mind the fact that in demyelinating disease there is no parallelism between the inflammatory reaction and the intensity of the degenerative changes. The perivascular infiltration is encountered in areas in which little or no substantial degeneration of the parenchyma is noticeable, not to mention the frequent presence of exudate in the meninges in areas not related to underlying degeneration.

It is disturbing that the same reaction can be interpreted as the result of two basically different processes. Such elasticity in the interpretation of the pathologic process leading to two opposing concepts of the same process may have resulted from lack of knowledge of a possible common

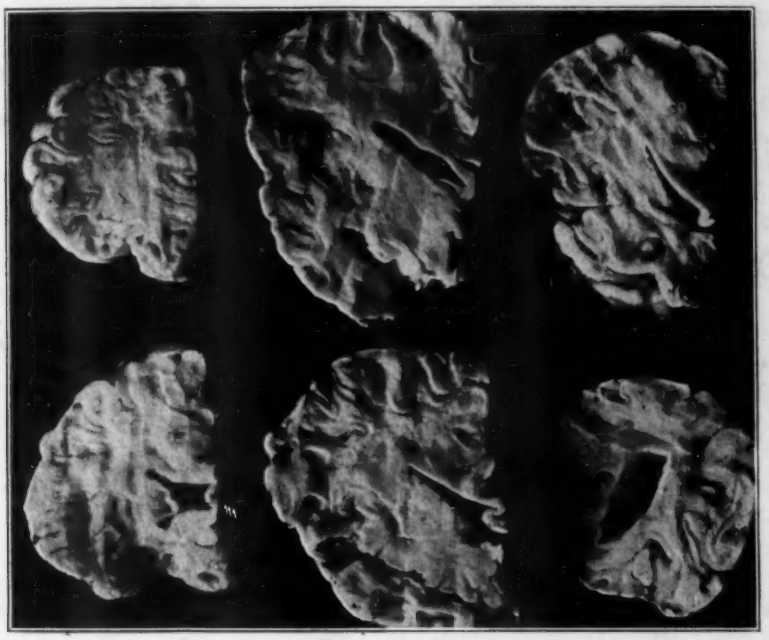


Fig. 28.—Extensive softening and necrosis at various levels. Scarlatinal encephalitis. Gross specimens.

link which would permit evaluation on the basis of variations of the same process, rather than of fundamental differences. Such a link might be furnished by the studies on experimental cerebral anaphylaxis. The comparison of this pathologic process to that of demyelinating diseases suggests, in my estimation, that a common denominator in the pathologic features may be found in an allergic reaction of the nerve tissue.

The pathologic changes associated with experimental cerebral anaphylaxis briefly reported in this paper have been utilized here as a comparative standard for the evaluation of the pathologic process of demyelinating disease. Emphasis has been placed on the analogy of the two conditions, with a view to establishing a possible common physiopathologic reaction.

It is true that one seldom observes with demyelinating diseases the outstanding hemorrhages typical of the Arthus phenomenon. One must, however, remember that such hemorrhages are characteristic only of the very acute and the very early stages of the reaction. It is also true that polymorphonuclear elements have rarely been reported in the perivascular exudate of demyelinating diseases, but one must remember that the leukocytes begin to disappear as soon as a few hours after the onset of the anaphylactic reaction and that gradually the polymorphonuclear cells are substituted by lymphocytes. Practically no leukocytes are present in the later stages, when the reaction has changed from a polymorphonuclear-hemorrhagic to a lymphocytic-histiocytic type.

In the acute, experimentally induced type of poliomyelitis the same changes occur. The exudate, which in the very early stages is formed of polymorphonuclear cells, changes into one of lymphocytes as the disease progresses. This change in the type of exudate is important because cases of human poliomyelitis have been reported in which the exudate was formed by lymphocytes, and not by polymorphonuclear cells. But even in the absence of polymorphonuclear leukocytes, Pette [110] formulated the concept that preceding the stage of lymphocytic infiltration there presumably always is, in the severe type at least, a stage of polymorphonuclear infiltration. He, however, expressed the possibility that in cases of mild poliomyelitis the stage of leukocytic infiltration may fail to appear. In cases of acute demyelinating diseases in which

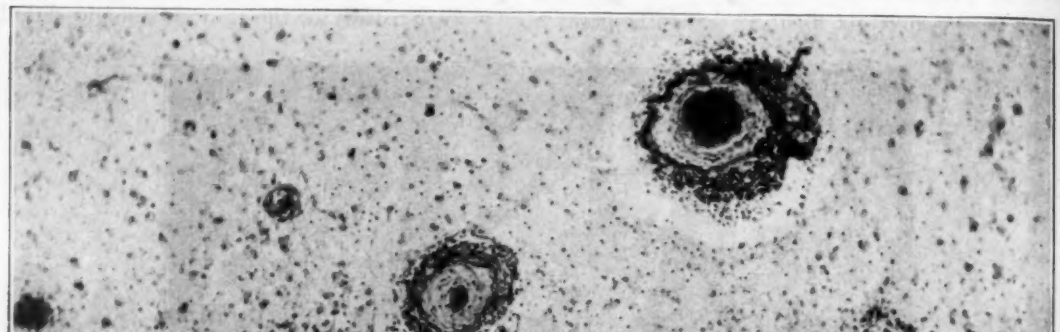


Fig. 29.—Thickening and degeneration of the blood vessel walls (from Ferraro [75]). Hematoxylin and eosin stain.

autopsy is generally performed several days after the onset of the disease, one should not be surprised at the absence of leukocytic infiltration.

As for the rest of the pathologic picture, both with anaphylaxis of the brain and with demyelinating diseases, acute or chronic, patchy or diffuse, there occur the same fundamental processes of edema, lymphatic stasis, necrosis, lymphocytic-histiocytic reaction, giant cell formation and repair.

None of these individual components of the histologic picture, taken separately, constitutes a characteristic or is pathognomonic of the anaphylactic reaction. However, evaluation of the histologic picture as a whole, with consideration for all the various components, constant or inconstant, should ultimately determine its interpretation.

It is my impression that unification of the pathologic syndrome of demyelinating diseases appears plausible as the expression of an allergic reaction of the nerve tissue. This unification has in its support the opinions expressed by investigators that from a clinical standpoint the demyelinating diseases are simply the expression of variations of the same fundamental process and the clinical impression as to their allergic nature already expressed.

The analogy of the cerebral pathology of demyelinating diseases and the pathology of cerebral anaphylaxis will open new avenues to the interpretation of the pathogenesis and histogenesis of multiple sclerosis, diffuse sclerosis and the acute encephalomyelitides.

The question arises now as to the factors responsible for the allergic reaction. The answer is difficult, especially in view of the fact that apparently different etiologic factors seem to result in the same clinicopathologic picture. The virus of vaccinia, of rabies, of measles, of influenza and of chickenpox, as well as the streptococcus of scarlet fever, all seem to bring about the same results. If one wishes to speculate on recent statements that a protein molecule constitutes the central nucleus of certain viruses, one could here find a possible explanation of the identity in type of cerebral reactions precipitated by various viruses.

On the other hand, the antigen may not necessarily originate from an infectious process. Products of intermediary metabolism could speculatively be held responsible for the production of antigens. Accurate dietary and metabolic studies in cases of demyelinating diseases might lead to the finding of additional etiologic factors, in the direction of allergic reactions rather than in that of deficiencies. The predominance of multiple sclerosis in certain geographic areas might also center around common dietary factors.

Esotoxins or endotoxins of bacteria, which are at the basis of the so-called Shwartzman phenomenon, or phenomenon of local sensitivity, may through the same mechanism result in allergic involvement of the cerebral tissue.

The importance of contributory factors in precipitating or aggravating an allergic reaction of the brain would also find its support. Some of these factors have been investigated experimentally. The contribution of Vaubel,[121] Knepper [122] and Knepper and Waaler [123] on the value of precipitating factors, such as fatigue and hyperventilation, the action of external agents, such as trauma, cold or heat, and the influence of endocrine products has demonstrated the importance of contributory factors in determining not only the intensity but the localization of the allergic reaction in certain organs.

Once the initial pathologic basis has been established in the brain, additional factors may play a role in the progress of the disease or in its phases of reactivation. I refer to the possible development of antigen (anaphylactogens) from the white or from the gray matter. The studies of Bailey and Gardner [132a] have established that antigenic substances can be derived from myelin sheaths. That the brain has immunologic properties which make that tissue almost as organ specific as the lens of the eyes is known. The brain-specific antigens, or haptens, have been claimed by some authors to have the properties of lipids only, whereas other authors (Bailey and Gardner) expressed the belief that the antigen of brain broth may be either a polysaccharide complex or a protein derivative.

Interpretation of the pathologic process of demyelinating disease on the basis of allergy could clarify the still existing confusion as to the significance of the perivascular and histiocytic reaction, so often disregarded or minimized in the study of the cerebral pathology, and might offer a common ground for evaluation of the vascular reaction as a whole under the term "hyperergic inflammation," already coined by Rossle, or of "reactive allergic inflammation," which I should like to propose.

Interpretation of the pathologic picture of demyelinating disease in the light of an allergic reaction does not exclude the histogenic origin of plaques through thrombus formation, as maintained by Putnam and his co-workers.

132a. Bailey, G. H., and Gardner, R. E.: Tissue Specificity of Brain and Medullated Nerves as Shown by Passive Anaphylaxis in the Guinea Pig, J. Exper. Med. **72**:499-510 (Nov.) 1940.

As far back as 1939 Putnam and Alexander,[59b] in discussing the cause of thrombus formation in demyelinating diseases, stated:

> The fact that similar "encephalomyelitides" may be provoked in animals by the injection of organ extracts and bacterial products furnishes a possible explanation for the postinfectious types. Some thrombi may be of "allergic" origin (Dietrich and Schröder, Alexander and Campbell). A great group remains, however, in regard to which there is no precise information.

In 1941 Putnam [133] again expressed the view that the origin of encephalomyelitis is in some sense an allergic reaction, adding that "it seems not unreasonable to suppose that an instability of the clotting mechanism of the blood might be one aspect of allergy."

That interference with circulation of the blood is part of the allergic reaction has been established experimentally by Doerr,[134] who reported that capillary and precapillary vessels react to anaphylactogen with changes in caliber (dilation and constriction) and with changes in permeability (edema and diapedesis).

Abell and Schenck,[71] using the transparent chamber technic devised by Clark and co-workers,[135] were able to compare the behavior of the arterioles, capillaries and venules of a normal rabbit with the corresponding vessels in the same rabbit after sensitization and injections of anaphylactogen. They observed that in a rabbit sensitized to horse serum, intravenous injection of this antigen may be followed by (*a*) arteriolar contraction with obliteration of the lumens of the arterioles and stoppage of the circulation, (*b*) increased adherence of leukocytes to the endothelium of the blood vessels and emigration of leukocytes through the walls of the capillaries and venules in large numbers and (*c*) sticking of leukocytes to each other to form clumps or emboli, which block the circulation in many capillaries and venules.

In addition to thrombosis, allergy may produce vascular damage in the form of periarteritis, intimal hyperplasia, fibrinoid degeneration of the intima and media (Fox and Jones [136]) and periarteritis nodosa (Vaubel,[121] Rich and Gregory [137]).

This vascular pathologic process, called hypergic arteritis by Vaubel, and leading to reduction or occlusion of the lumen of the blood vessels, was also reported by Knepper and Waaler,[123] in an article on functional hyperactivity of the lungs and heart in the course of experimental allergy.

Vasospasm in the course of allergy was advocated by Gerlach [117] and by Knepper and Waaler,[123] and mechanical occlusion of capillaries resulting from surrounding edema was predicated by Gerlach.

It is certain that variability of the coagulation time accompanies allergic reactions. However, there seems to be a difference of opinion as to whether the coagulation time is shortened or prolonged (Urbach and Gottlieb [138]). In the so-called hemoclastic crisis of Widal, there are, for instance, decrease in the leukocyte count, relative lymphocytosis, decrease in the amount of protein colloids, lowering of blood pressure and increase in coagulability of the blood.

The unification of the pathologic changes in the brain under the heading of allergic reaction would offer a new avenue of interpretation in the field of prevention and therapy of the important group of demyelinating diseases on an immunologic basis. In this connection, Horton, Wagener, Aita and Woltman,[139] of the Mayo Clinic, have made a preliminary report of their attempts to treat multiple sclerosis, especially in the acute stage, with intravenous injections of histamine. The authors seem inclined to relate any recovery and improvement to vasodilatation in the central nervous system resulting from repeated injections of histamine. One could, however, speculate on another explanation of the beneficial effect of histamine, based on the work of Fell, Rodney and Marshall [140] and of

133. Putnam, T. J.: Newer Concepts of Postinfectious and Related Forms of Encephalitis, Bull. New York Acad. Med. **17**:337-347 (May) 1941.

134. Doerr, R.: Allergische Phänomene, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, vol. 13, p. 650.

135. Clark, E. R.; Clark, E. L., and Williams, R. G.: Microscopic Observations in the Living Rabbit of the New Growth of Nerves and the Establishment of Nerve-Controlled Contractions of Newly Formed Arterioles, Am. J. Anat. **55**:47, 1934. Clark, E. R., and Clark, E. L.: Observations on Changes in Blood Vascular Endothelium in the Living Animal, ibid. **57**: 385, 1935.

136. Fox, R. A., and Jones, L. R.: Vascular Pathology in Rabbits Following Administration of Foreign Protein, Proc. Soc. Exper. Biol. & Med. **55**:294, 1944.

137. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65, 1943.

138. Urbach, E., and Gottlieb, P. M.: Allergy, New York, Grune & Stratton, Inc., 1943.

139. Horton, B. T.; Wagener, H. P.; Aita, J. A., and Woltman, H. W.: Treatment of Multiple Sclerosis by the Intravenous Administration of Histamine, J. A. M. A. **124**:800 (March 18) 1944.

140. Fell, N.; Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes: Synthesis and Immunologic Investation; I. Histamine-Azoprotein, J. Immunol. **47**:237, 1943.

Cohen and Friedman [141] on the production of histamine-specific antibodies by the use of histamine as a specific hapten conjugated by an inert protein carrier. In the experience of Fell and associates, histamine-specific antibodies were sufficient to prevent the anaphylactic shock resulting from intravenous injection of a shock-producing dose of protein. The prevention of the anaphylactic shock might be related to neutralization or destruction of the hypothetically liberated histamine. It is this explosive liberation of histamine which, according to Dale, is the cause of the anaphylactic shock.

141. Cohen, B. M., and Friedman, H. G.: Antibodies to Histamine Induced in Human Beings by Histamine Conjugates, J. Allergy **14**:195, 1943.

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THE HUMAN PYRAMIDAL TRACT

X. THE BABINSKI SIGN AND DESTRUCTION OF THE PYRAMIDAL TRACT

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CHARLESTON, S. C.

The Babinski toe sign is regarded by many clinicians as the most important superficial reflex used in neurologic diagnosis because it is thought to be indicative of destruction of the pyramidal tract. There is difference of opinion as to whether irritation of the bundle can also produce the reflex. Many physicians believe that there is scarcely a neurologic sign with less possibility of error. No matter how transient the Babinski sign, it is thought by some clinicians that it is evidence of a lesion involving the pyramidal tract and that even an equivocal sign may be regarded as of as great significance as an actual positive response.

If both irritation and destruction produce a Babinski sign, there must be diametrically opposite nervous phenomena which act on the anterior horn cells of the first sacral segment of the cord, namely, hyperactivity and hypoactivity of the pyramidal tract. According to this concept, any alteration in the conductive activity of the pyramidal tract should produce the Babinski sign. There is experimental evidence in the literature that the pyramidal tract conducts according to a pattern of so many waves per second. The following question arises: "Can interruption of the normal rhythm of pyramidal tract impulses by neurologic or systemic disease cause a physiologic block and thus a positive Babinski sign?" Physiologic block would certainly have the same effect on the cells of the lower motor neuron as loss of fibers. If this premise can be shown to be true, then one may have a sound neurologic explanation for the appearance of transient paralyses, for the instances of a brief and fluctuating Babinski sign and for the speedy functional recoveries frequently observed in medical practice which are not now adequately explained.

By definition, the pyramidal tracts consist of all the fibers which pass through the pyramids of the medulla oblongata. This definition does not take into consideration either the origin or the termination of the fibers. It is known that the pyramidal tracts have a central origin from the cerebral cortex, that they are condensed in the central portion of the internal capsules, that they course in close relation to the lateral ventricles, which frequently are affected by various degrees of internal hydrocephalus or hemorrhage and that in the brain stem and the spinal cord they are in a peripheral and exposed position. Because of these topographic relations, the pyramidal tract is probably very vulnerable to involvement by neurologic disease. It is the longest, largest and one of the most exposed tracts in the central nervous system. It is the last to develop ontogenetically and phylogenetically. The Netherland school of neurologists regards this late development of the pyramidal fasciculus as an important factor in its susceptibility to disease processes.

I believe it may be in order to assume that lesions, in some instances at least, may produce a physiologic block of pyramidal tract impulses and then to attempt to break down or confirm the hypothesis by scientific investigation. For many years the neighborhood symptoms or the remote effects of sometimes small lesions in the brain and cord have presented a baffling phenomenon, and numerous theories have been formulated to explain them.

The present paper is a summary of the evidence concerning correlation of the Babinski sign and destruction of the pyramidal tract contained in the literature, especially that published in American journals.

RESULTS

Observations with respect to the characteristics of the sign of Babinski in about 1,000 cases will be described under the following headings: (1) normal status, (2) drugs, (3) hypoglycemia, (4) sleep and narcolepsy, (5) epilepsy, (6) circulatory disturbances, (7) tumors, (8) inflammatory processes and (9) miscellaneous conditions.

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Normal Status.[1]—The Babinski sign may be elicited in persons who have no other manifestations of neurologic disease. In control studies it was found that hospital patients with nonneurologic symptoms and patients with a history of head injury showed the Babinski sign in the ratio of about 4:100. On the whole, older persons were more susceptible than young ones. About 1.25 per cent of a large group of inductees between the ages of 21 and 35 exhibited the Babinski sign on proper stimulation. In severe physical exertion, such as that induced by forced marching, the Babinski sign may manifest itself in young, apparently normal, men. One observer, however, stated that the classic Babinski sign, with fanning of the toes, can never be elicited in normal persons.

Drugs.[2]—There are drugs which can either produce the sign of Babinski in normal subjects or modify it when present in diseased persons. Among the compounds found in this study which can produce the Babinski sign are nitrous oxide, sodium amytal, barbital, general anesthetics, scopolamine, metrazol, bromide, tryparsamide and strychnine. The following report is based on several hundred cases:

Nitrous oxide produces a bilateral Babinski sign, which appears immediately after the crisis. This drug has a definite narcotic action on nerve cells, which is accentuated by anoxemia.

When sodium amytal is given intravenously, the Babinski sign can be elicited consistently just before unconsciousness occurs. This drug seems to act as an inhibitor of the activity of nerve cells, affecting the various divisions of the nervous system in the reverse order of their phylogenetic appearance. Barbital, in the same group, also produces a positive Babinski sign, especially when given in overdoses.

Scopolamine hydrobromide in doses of 0.001 Gm. may produce an extensor response in a normal person. In smaller doses, 0.0003 Gm., it brings out a latent Babinski response. This drug is a primary depressant of the central nervous system and, as such, decreases muscular tone. Physostigmine, on the other hand, abolishes the Babinski reflex. With scopolamine, extension of the big toe may last for only a few minutes, but sometimes it may remain for hours. Epileptic patients appear to be more susceptible to injections of scopolamine, an observation which may indicate a relative deficiency of the pyramidal tract in such patients.

In a few cases opium, strychnine, the general anesthetics and the bromides were reported to produce a transient Babinski sign.

Hypoglycemia.[3]— Hypoglycemia, whether it occurs spontaneously, as the result of an adenoma

1. Davison, H. A.: Plantar Reflexes in Normal Adults, Arch. Neurol. & Psychiat. **26**:1027-1037 (Nov.) 1931. Savitsky, N., and Madonick, M. J.: Statistical Control Studies in Neurology: I. The Sign of Babinski, ibid. **49**:272-276 (Feb.) 1943. Yakovlev, P. I., and Farrell, M. J.: Influence of Locomotion on the Plantar Reflex in Normal and in Physically and Mentally Inferior Persons: Theoretic and Practical Implications, ibid. **46**:322-330 (Aug.) 1941.

2. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129-245, 1936. Curran, F. J.: A Study of Fifty Cases of Bromide Psychosis, J. Nerv. & Ment. Dis. **88**:163-192, 1938. Delgado, H.: Treatment of Schizophrenia with Cardiazol in Convulsant Doses, ibid. **89**:625-639, 1939. Finkelman, I.; Steinberg, D. L., and Liebert, E.: Treatment of Schizophrenia with Metrazol by Production of Convulsions, J. A. M. A. **110**:706-709 (March 5) 1938. Gyárfás, K.: Correlations of Athetosis, Catatonia and Hypoglycemia, J. Nerv. & Ment. Dis. **87**: 588-597, 1938. Hodskins, M. B., and Yakovlev, P. I.: Neurosomatic Deterioration in Epilepsy, Arch. Neurol. & Psychiat. **23**:986-1031 (May) 1930. Lichtenstein, B. W.: Acute and Subacute Toxic Myelopathies Following Therapy with Arsphenamines, ibid. **48**:740-760 (Nov.) 1942. Low, A. A.; Sonenthal, I. R.; Blaurock, M. F.; Kaplan, M., and Sherman, I.: Metrazol Shock Treatment of the "Functional" Psychoses, ibid. **39**:717-736 (April) 1938. Marinesco, G., and Nicolesco, M.: Modifications of Postural Tonus with Babinski Sign After Injections of Scopolamine in Extrapyramidal Hypertonia, Rev. neurol. **1**:246-249, 1927. Pamboukis, G., and Tsiminakis, J.: Cardiazol Treatment in Schizophrenia, Encéphale **2**:94-103, 1938; abstracted, J. Nerv. & Ment. Dis. **96**:717-718, 1942. Purves-Stewart, J.: Cisternal and Lumbar Drainage in the Treatment of Coma from Acute Barbital Poisoning, Together with Observations on Chronic Barbital Poisoning, Jahrb. f. Psychiat. u. Neurol. **51**:203-213, 1934. Thorner, M. W.: The Psycho-pharmacology of Sodium Amytal, J. Nerv. & Ment. Dis. **81**:161-167, 1935. Tournay, A.: The Babinski Sign: Its Characteristics, Mechanism and Significance, Arch. Neurol. & Psychiat. **17**:834-835 (June) 1927. von Thurzo, E.: Ueber einige neuere diagnostische und therapeutische Verfahren in der Neurologie, Berlin, S. Karger, 1929. Zador, J.: Conditions Affecting and the Pathogenesis of the Babinski Reflex, Monatschr. f. Psychiat. u. Neurol. **64**:336, 1927; abstracted, Arch. Neurol. & Psychiat. **20**:847-848 (Oct.) 1927.

3. Bassoe, P., and Traut, E.: The Neurologic Manifestations of Insulin Reactions, Arch. Neurol. & Psychiat. **21**:238-240 (Jan.) 1929. Feinier, L.: Neuropsychiatric Symptomatology in a Case of Hypoglycemia, ibid. **32**:1350-1353 (Dec.) 1934. Fortuyn, J. D.: Hypoglycemia and the Autonomic Nervous System, J. Nerv. & Ment. Dis. **93**:1-15, 1941. Freed, H., and Saxe, E.: Prolonged Nonhypoglycemic Coma Occurring During the Course of Insulin Shock Therapy, ibid. **90**:216-226, 1939. Frostig, J. P.: Insulin Therapy of Schizophrenia, Schweiz. Arch. f. Neurol. u. Psychiat. **39**:153-157, 1938. Greenwood, J.: A Case of Psychosis Due to Hypoglycemia, Arch. Neurol. & Psychiat. **33**: 232-234 (Feb.) 1935. Heiman, M.: Significance of Babinski Sign During Hypoglycemic Treatment of Schizophrenia, Am. J. Psychiat. **96**:387-391, 1939. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypo-

(Footnotes continued on next page)

of the pancreas, or is caused by an overdose of insulin or is induced in shock therapy for schizophrenia, may produce a Babinski sign. Several hundred cases in which hypoglycemia was the factor involved occurred in the present series. The underlying mechanism in hypoglycemia appears to be a decrease in the oxygen consumption of the cerebral cortex, which results in anoxemia of the nerve tissue. The Babinski sign can be elicited prior to, during or after the period of coma; it may be transient or may last for hours or days. One patient exhibited a Babinski sign for thirteen days after hypoglycemic shock therapy. Extension of the toe may appear first on one side and then on the other. Transient hemiplegias have been described as being present for several hours.

Sleep.[4]—The Babinski sign can be elicited in normal persons during ordinary sleep or during the sleep following prolonged experimental insomnia. In young adults subjected to experimental insomnia a Babinski sign was invariably elicited on plantar stimulation in the period of sleep following the insomnia. There was not only extension but spreading of all the toes, and the reflex could be obtained any number of times provided a short period of rest was allowed between successive stimulations. On several occasions, a crossed, as well as a direct, Babinski reflex could be observed. All the tests were made without the sleeper's being wakened.

Narcolepsy and Catalepsy.[5]—A transitory Babinski sign has been reported in cases of both narcolepsy and catalepsy. An extensor response was noted in 1 patient with dementia precox who was in a catatonic state. Chronaxia studies on this patient showed that the chronaxia during the period of elicitation of the Babinski sign was greater in the extensor than in the flexor muscle. When the Babinski sign was reversed to normal flexion on stimulation of the sole, the chronaxia of the extensor proprius muscle was less than the chronaxia of the flexor brevis muscle. This indicates a transitory modification of nerve functions associated with dementia precox which disclosed itself in a fleeting pyramidal disorder.

Epilepsy.[6]—The Babinski sign has been elicited during and after either the jacksonian or the idiopathic type of epilepsy. After the period of plantar areflexia in the attack, there is a slight extensor movement of the big toe, and eventually a classic Babinski sign appears. Monoplegia, hemiplegia and central and ocular palsy or aphasia, usually regressive, but occasionally permanent, may follow an epileptic seizure. Although the Babinski reflex cannot generally be elicited between the attacks, smaller doses of scopolamine are required to produce it than are needed for normal persons, an indication of a relative weakness or deficiency of the pyramidal tract in the epileptic patient. Sensory influence in the production of an epileptic seizure was indicated in a case in which tactile stimulation of

glycemic Treatment for Schizophrenia, Arch. Neurol. & Psychiat. **39**:853-858 (April) 1938; Biochemical Changes Occurring in the Cerebral Blood During the Insulin Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **89**:273-293, 1939. Klapman, J. W., and Weinberg, M. H.: Cerebral Insult Following Hypoglycemic Shock Therapy with Recovery, Illinois M. J. **79**:236-237, 1941. Murphy, F. D., and Purtell, J.: Insulin Reaction and Brain Damage in Diabetes, Am. J. Digest. Dis. **10**:103-107, 1943. Ravid, J. M.: Transient Insulin Hypoglycemic Hemiplegias, Am. J. M. Sc. **175**:756-769, 1928. Read, C. F.; Heilbrunn, G., and Liebert, E.: Studies in the Insulin Treatment of Dementia Praecox, J. Nerv. & Ment. Dis. **90**:747-756, 1939. Reese, H. H.: Experiences with Insulin Shock Therapy in Schizophrenia, Arch. Neurol. & Psychiat. **38**:907-908 (Oct.) 1937. Reese, H. H., and Veer, A. V.: Experiences with Insulin Shock Therapy, ibid. **39**:702-716 (April) 1938. Sakel, M.: The Pharmacological Shock Treatment of Schizophrenia, translated by J. Wortis, Washington, D. C., Nervous and Mental Disease Publishing Company, 1938. Wadsworth, R. C., and McKeon, C.: Pathologic and Mental Alterations in a Case of Simond's Disease, Arch. Neurol. & Psychiat. **46**:277-296 (Aug.) 1941. Weil, A. A.: A Contribution to the "Quick-Motion-Picture" Illusion of Hoff-Pötzl, J. Nerv. & Ment. Dis. **93**:42-52, 1941. Ziskind, E.: Hyperinsulinism with Report of a Case, Arch. Neurol. & Psychiat. **26**:870-872 (Oct.) 1931.

4. Kleitman, N.: Studies on the Physiology of Sleep: I. The Effects of Prolonged Sleeplessness on Man, Am. J. Physiol. **66**:67-92, 1923. Savitsky, N., and Madonick, M. J.: Statistical Control in Neurology: I. The Sign of Babinski, Arch. Neurol. & Psychiat. **49**:272-276 (Feb.) 1943. Tournay, A.: The Babinski Sign: Its Characteristics, Mechanism and Significance, ibid. **17**:834-835 (June) 1927.

5. Jones, M. S.: A Case of Recurrent Attacks of Prolonged Sleep, J. Neurol. & Psychopath. **16**:130, 1935; abstracted, Arch. Neurol. & Psychiat. **38**:861-862 (Oct.) 1937. Redlich, E.: The Question of Narcolepsy, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:128, 1931; abstracted, Arch. Neurol. & Psychiat. **28**:173-175 (July) 1932. Wortis, S. B., and Kennedy, F.: Narcolepsy, Am. J. Psychiat. **12**:939-946, 1933.

6. Benon, R., and LeFevre, G.: A Case of Traumatic Dementia, Arch. Neurol. & Psychiat. **10**:242-243 (Aug.) 1923. Hodskins, M. B., and Yakovlev, P. I.: Neurosomatic Deterioration in Epilepsy: A Clinicopathologic Contribution to the Concept with a Report of Two Cases, ibid. **27**:113-137 (Jan.) 1932. Scarff, J. E.: Pseudojacksonian Epilepsy in Children, ibid. **49**:223-236 (Feb.) 1943. Strauss, H.: Jacksonian Seizures of Reflex Origin, ibid. **44**:140-152 (July) 1940. Tournay, A.: Behavior of the Plantar Reflex in Jacksonian Epilepsy, with Some Observations on the Pathologic Physiology of the Babinski Sign, ibid. **13**:592-595 (May) 1925. Weingrow, S. M.; Fitch, T. S. P., and Pigott, A. W.: Some Clinical Neurological Findings in Epilepsy, J. Nerv. & Ment. Dis. **88**:281-306, 1938.

the skin or mucous membrane on any part of the right side of the body initiated a jacksonian attack with a Babinski sign. During periods of improvement the Babinski sign disappeared.

Circulatory Disturbances.[7]—There is abundant evidence in the literature that the pyramidal

7. Abbott, K. H.: Amnesic Aphasia Due to Two Small Focal Lesions, Bull. Los Angeles Neurol. Soc. **3**: 188-190, 1938. Ahrens, R. S.: Neurologic Aspects of Primary Anemia, Arch. Neurol. & Psychiat. **28**:173-175 (July) 1932. Allison, R. S., and Morison, J. E.: Cerebral Vascular Lesion and the Tentorial Pressure Cone, J. Neurol. & Psychiat. **4**:1-10, 1941. Alpers, B. J.: Ventricular Hemorrhage with Recovery: Report of a Case, Arch. Neurol. & Psychiat. **12**:695-700 (Dec.) 1924. Austregesilo, A.: Nervous Disorders in Certain Tropical Diseases, Rev. neurol. **1**:1-21, 1927; abstracted, Arch. Neurol. & Psychiat. **18**:596-599 (Oct.) 1927. Bagley, C.: Spontaneous Cerebral Hemorrhage, ibid. **27**:1131-1174 (May) 1932. Burley, B. T.: Two Cases of Cerebral Hemorrhage in Young Adults, ibid. **9**:803-807 (June) 1923. Cohen, I.: Chronic Subdural Accumulations of Cerebrospinal Fluid After Cranial Trauma: Report of a Case, ibid. **18**:709-723 (Nov.) 1927. Cooper, M. J.: Transient Hemiplegia in a Syphilitic Patient of Twenty-Eight, ibid. **28**:218-221 (July) 1932. Courtney, J. W.: Case of Myelitis of Unusual Etiology, ibid. **18**:482-485 (Sept.) 1927. Dimitri, V.: Superior Alternating Hemiplegia, Rev. Asoc. méd. argent. **53**:1109-1113, 1939. Dohan, F. C.: A Case of Occlusion of the Sylvian Artery, Arch. Neurol. & Psychiat. **29**:1369-1370 (June) 1933. Freedberg, A. S., and Sloan, L. H.: Association of Carotid Sinus Reflexes with Syncope and Convulsions, ibid. **38**:761-774 (Oct.) 1937. Globus, J.: Probable Topographic Relations of the Sleep-Regulating Center, ibid. **43**:125-138 (Jan.) 1940. Gordon, A.: Painful Hemiplegia: A Consideration of Central Pain, ibid. **38**:211-214 (July) 1937. Griffith, J. Q.: Involvement of the Facial Nerve in Malignant Hypertension, ibid. **29**:1195-1202 (June) 1933. Hadden, S.: Neurological Symptoms in Posthemorrhagic Secondary Anemia, Ann. Int. Med. **9**:1572-1577, 1936. Hadden, S., and Wilson, G.: Objective Symptoms of Involvement of the Spinal Cord in Cases of Pernicious Anemia Removed with Treatment, Arch. Neurol. & Psychiat. **36**:888-890 (Oct.) 1936. Hyland, H. H.: Thrombosis of Intracranial Arteries: Report of Three Cases Involving, Respectively, the Anterior Cerebral, Basilar and Internal Carotid Arteries, ibid. **30**:342-356 (Aug.) 1933. Hyland, H. H., and Farquharson, R. F.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, ibid. **36**:1166-1205 (Dec.) 1936. Hyndman, O.: Physiology of the Spinal Cord: I. Role of the Anterior Column in Hyperreflexia, ibid. **46**:695-703 (Oct.) 1941; II. Influence of Chordotomy on Existing Motor Disturbances, J. Nerv. & Ment. Dis. **98**:343-358, 1943. Hyndman, O., and Wolkin, J.: Anterior Chordotomy: Further Observations on Physiologic Results and Optimum Manner of Performance, Arch. Neurol. & Psychiat. **50**:129-148 (Aug.) 1943. Jefferson, G.: Bilateral Rigidity in Middle Meningeal Hemorrhage, Brit. M. J. **2**:683-685, 1921. Kampmeier, R. H.: Sickle Cell Anemia as a Cause of Cerebral Vascular Disease, Arch. Neurol. & Psychiat. **36**:1323-1329 (Dec.) 1936. King, A. B., and Langworthy, O. R.: Neurologic Symptoms Following Extensive Occlusion of the Common or Internal Carotid Artery, ibid. **46**:835-842 (Nov.) 1941. Krabbe, K. H.: Facial and Meningeal Angiomatosis Associated with Calcifications of the Brain Cortex, ibid. **32**:736-755 (Oct.) 1934. Leopold, S. S.: Ruptured Aneurysm at Junction of Right Anterior Communicating and Anterior Cerebral Arteries, ibid. **31**:605-610 (March) 1934. Levinson, A.: Acute Transitory Cerebral Manifestations in Infants and in Children, J. A. M. A. **101**:765-770 (Sept. 2) 1933. Lhermitte, J., and Trelles, J. O.: Physiology and Physiopathology of the Corpus Striatum and Subthalamic Region, Encéphale **27**:235-271, 1932; abstracted, Arch. Neurol. & Psychiat. **29**:874-876 (April) 1933. McConnell, A. A.: Intracranial Conditions After Closed Head Injuries, Brain **65**:266-280, 1942. McGovern, F. H.: Cerebral Air Embolism Following Antral Irrigation, Arch. Otolaryng. **34**:593-595 (Sept.) 1941. Pilcher, C.: Subcortical Hematoma: Surgical Treatment, with Report of Eight Cases, Arch. Neurol. & Psychiat. **46**: 416-430 (Sept.) 1941. Priest, W. M.: Epidural Hemorrhage Due to Hemophilia Causing Compression of the Spinal Cord, Lancet **2**:1289, 1935; abstracted, Arch. Neurol. & Psychiat. **37**:1189 (May) 1937. Putnam, T. J.: Section of the Extrapyramidal Tracts in the Treatment of Dystonia Musculorum Deformans, ibid. **28**:208-210 (July) 1932. Quincke, H.: Acute Circumscribed Edema and Related Conditions, Med. Klin. **17**: 675, 1921; abstracted, Arch. Neurol. & Psychiat. **6**: 682-684 (Dec.) 1921. Rangell, L.: Cerebral Air Embolism, J. Nerv. & Ment. Dis. **96**:542-555, 1942. Reider, N.: Neuropsychiatric Complications Following Severe Loss of Blood, Arch. Neurol. & Psychiat. **44**:1069-1075 (Nov.) 1940. Remond, A., and Colombies, H.: Hemiplegia with Hemichorea, Rev. de méd. **39**:107, 1922; abstracted, Arch. Neurol. & Psychiat. **9**:103-104 (Jan.) 1923. Romano, J., and Evans, J. W.: Symptomatic Psychosis in a Case of Secondary Anemia, Arch. Neurol. & Psychiat. **39**:1294-1301 (Dec.) 1938. Rossen, R.; Kabat, H., and Anderson, J. P.: Acute Arrest of Cerebral Circulation in Man, ibid. **50**:510-528 (Nov.) 1943. Sands, I. J.: Aneurysm of the Right Posterior Communicating Artery of the Circle of Willis Producing the Syndrome of Alternating Oculomotor Hemiplegia, ibid. **14**:554-558 (Oct.) 1925; Aneurysm of Cerebral Vessels: Clinical and Pathologic Presentation, ibid. **19**:732-734 (April) 1928; Aneurysms of the Cerebral Vessels, ibid. **21**:37-46 (Jan.) 1929. von Sarbó, A.: Aneurysms of the Dura Mater, ibid. **22**:1-4 (July) 1929. Scott, M.: Trigemino-Auricular Reflex, ibid. **43**:181-182 (Jan.) 1940. Shallow, T., and Burns, M. A.: A Case of Thrombosis of the Vertebral, Basilar and Internal Carotid Arteries, ibid. **31**:455-458 (Feb.) 1934. Sherman, I. C., and Krumholz, S.: A Case of Intradural Hematoma with Ipsilateral Hemiplegia and Ipsilateral Third Nerve Palsy, J. Nerv. & Ment. Dis. **95**:176-182, 1942. Steiner, G.: Chronic Perivascular Demyelination (Homophasic Cerebrospinal Demyelinating Periangiosis), Arch. Neurol. & Psychiat. **41**:166-178 (Jan.) 1939. Stephenson, J. W.: Disappearance of Tremor in a Case of Paralysis Agitans Following an Attack of Hemiplegia, with Comments on the Production of the Tremor in Paralysis Agitans, ibid. **23**: 199-201 (Jan.) 1930. Stief, A.: A Case of Hemiatrophy of the Face with Autopsy Observations, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:573, 1933; abstracted, Arch. Neurol. & Psychiat. **31**:1107-1108 (May) 1934. von Stockert, F. G.: A Case of Bilateral Occlusion of the Posterior Cerebral Artery, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **34**:23, 1932; abstracted, Arch. Neurol. & Psychiat. **30**:1372-1373 (Dec.) 1933. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage, ibid. **27**:1080-1132 (May) 1932. Teitelbaum, H. A.; Langworthy,

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bundle can be affected by the blood stream in many other ways than by hemorrhage, thrombosis or embolism of vessels within the central nervous system.

Acute massive hemorrhage or chronic loss of blood in any portion of the body may apparently cause paralytic symptoms, with the Babinski sign. This reflex has been reported in cases of gastric hemorrhage, hemorrhoids, hemoptysis of the lungs and postpartum hemorrhage. Blood transfusion alleviates the paralysis and reverses the extensor toe reflex to the normal response in the early stages. Sometimes hemiplegia may not make itself evident for as long as thirty-six hours after the onset of the hemorrhage. Prolonged bleeding, however, may produce permanent damage. A red blood cell count of approximately 2,000,000 or lower, is mentioned as being the critical level below which paralysis, with the Babinski sign, may appear.

Hemiplegia, with a Babinski sign, has been reported in persons with extremely low blood pressure. It is believed that in such cases the blood is not pumped adequately to the cerebral cortex, which creates anoxemia in the brain.

Temporary circulatory arrest produced the Babinski sign in 2 of 10 cases, but it could not be induced a second time. Cerebral air embolism has been described as producing temporary paralysis and the Babinski sign. In some instances the air may be absorbed before any permanent motor deficit is in evidence.

Too many red blood cells, as in polycythemia or leukemia, or too few, as in the secondary anemias or in pernicious anemia, may produce the Babinski sign. Abnormal cell types, such as are present in sickle cell anemia or malaria, likewise may cause anoxemia of the brain, with a resultant Babinski sign. Changes in the oxygen–carbon dioxide–combining power of the hemoglobin, such as those associated with carbon monoxide poisoning or Cheyne-Stokes respiration, can produce a temporary Babinski sign.

An oversensitive carotid sinus reflex has been observed to cause periodic temporary hemiplegia, with the Babinski sign. In the hands of some clinicians, denervation has mitigated the defects. Section of the cervical sympathetic fibers in a patient with hemiplegia was followed by recovery, including the disappearance of the pathologic Babinski reflex.

Free blood in the subarachnoid space due to ruptured cerebral aneurysm, or from other causes, will in some instances cause temporary hemiplegia, with the Babinski sign. This is usually explained as due either to an irritating effect of the blood or to pressure. Blood when present on the convex surface of the cerebral cortex supposedly acts on the so-called motor cortex, whereas when present on the base of the brain it is thought to produce its effects by acting on the exposed pyramids of the medulla. Blood in the form of hematoma must produce its paralytic effects mainly by pressure. When the blood is removed, either in the free state or in the form of hematoma, recovery from all symptoms often occurs. Spontaneous recovery also may follow subarachnoid bleeding. Hemorrhage or blocked accumulations of cerebrospinal fluid in the lateral ventricles evidently produce a Babinski sign by pressure on the pyramidal tract fibers as they pass through the internal capsule.

Acute swelling of the brain or edema may also cause paralytic signs and symptoms, among which is the Babinski sign. On subsidence of the edema, the signs disappear in many cases. Neighborhood or contralateral effects are frequently explained on this basis, the latter occurring especially in the brain stem and the spinal cord. The transient Babinski reflex observed in cases of lobotomy or anterior chordotomy can be best defended on the basis of this phenomenon.

Tumors.[8]—Certain patients with tumor of the central nervous system who had classic signs

O. R., and King, A. B.: Apraxia: Report of a Case with Autopsy, ibid. **48**:469-475 (Sept.) 1942. Tournay, A.: Cheyne-Stokes Respiration and Periodic Babinski Sign, ibid. **18**:652 (Oct.) 1927. Tournay, A., and Holtzhauser, R.: Posterolateral Sclerosis Following Massive Hemorrhage, ibid. **29**:1368-1369 (June) 1933. Tureen, L. L.: Lesions of the Fundus Associated with Brain Hemorrhage, ibid. **42**:664-678 (Oct.) 1939. Urechia, C. I.: Pseudotumor Syndrome Dependent on Acute Swelling of the Brain, Rev. neurol. **27**:1185, 1920; abstracted, Arch. Neurol. & Psychiat. **8**:696-697 (Dec.) 1922. Watts, J. W., and Freeman, W.: Psychosurgery: Effect on Certain Mental Symptoms of Surgical Interruption of Pathways in the Frontal Lobe, J. Nerv. & Ment. Dis. **88**:589-601, 1938. Wertham, F.; Mitchell, N., and Angrist, A.: The Brain in Sickle Cell Anemia, Arch. Neurol. & Psychiat. **47**:752-767 (May) 1942. Wetherell, F. S.: Cervicodorsal Sympathectomy in Multiple Sclerosis: Its Rationale and Report of Eight Cases, ibid. **34**:99-110 (July) 1935. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During the Early Stages, ibid. **31**:956-986 (May) 1934.

8. Allen, S. S., and Lovell, H. W.: Tumors of the Third Ventricle, Arch. Neurol. & Psychiat. **28**: 990-1006 (May) 1932. Alpers, B. J., and Groff, R. A.: Parasellar Tumors: Meningeal Fibroblastomas Arising from the Sphenoid Ridge, ibid. **31**:711-736 (April) 1934. Alpers, B. J., and Yaskin, J. C.: Gliomas of the Pons: Clinical and Pathologic Characteristics, ibid. **41**:435-459 (March) 1939. Andersen, C.: Cushing's Syndrome: Hypophysial Basophilism, J. belge de neurol. et de psychiat. **35**:148, 1935; abstracted, Arch. Neurol. & Psychiat. **36**:423 (Aug.) 1936. Aronson, L.: Clinical Report of a Case of Intramedullary Neoplasm of

(Footnotes continued on next page)

the Spinal Cord; Operation; Deep X-Ray Therapy; Marked Improvement, ibid. **21**:233-235 (Jan.) 1929. Bailey, P., and Oldberg, E.: An Unusual Tumor of the Cerebellum: Report of a Case, ibid. **48**:149-150 (Dec.) 1942. Bogaert, L. V.: The Thalamic and Parkinsonian Types of Infundibular Tumors: The Occurrence of Glycoregulatory and So-Called Endocrine Disorders, ibid. **19**:377-393 (March) 1928. Burns, M. A.: Relative Value of Diagnostic Measures in the Localization of Tumors of the Brain, ibid. **20**:627-634 (Sept.) 1928. Courville, C. B.: Ganglioglioma: Tumor of the Central Nervous System; Review of the Literature and Report of Two Cases, ibid. **24**:439-491 (Sept.) 1930; Gangliogliomas: A Further Report with Special Reference to Those Occurring in the Temporal Lobe, ibid. **25**:309-326 (Feb.) 1931. Cushing, H., and Ayer, J. B.: Xanthocromia and Increased Protein in the Spinal Fluid Above Tumors of the Cauda Equina, ibid. **10**:167-193 (Aug.) 1923. Dandy, W. E.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle), ibid. **25**:44-66 (Jan.) 1931. Denker, P. G., and Osborne, R. L.: Aberrant Thyroid Tumor of the Vertebrae with Compression of the Spinal Cord: Recovery After Operation and High Voltage Roentgen Therapy, ibid. **49**:277-281 (Feb.) 1943. Ecker, A.: Removal of Tumor Arising Anterior to the Medulla, ibid. **46**:908-912 (Nov.) 1941. Elsberg, C. A.: The False Localizing Signs of Spinal Cord Tumor, ibid. **5**:64-79 (Jan.) 1921. Elsberg, C. A., and Globus, J. H.: Tumors of the Brain with Acute Onset and Rapidly Progressive Course, ibid. **21**:1044-1078 (May) 1929. Elsberg, C. A., and Strauss, I.: Tumors of the Spinal Cord Which Project into the Posterior Cranial Fossa, ibid. **21**:261-273 (Feb.) 1929. Favill, J.: Two Specimens of Occipital Lobe Lesions, ibid. **10**:115-118 (July) 1923. Fay, T.: Vasomotor and Pilomotor Manifestations: Their Localizing Value in Tumors and Lesions of the Spinal Cord; a Report of Thirteen Verified Cases, ibid. **19**:31-46 (Jan.) 1928; A Case of Gumma of the Brain with Onset of Symptoms Following Trauma: Operative Removal with Recovery, ibid. **22**:169-170 (July) 1929. Ferber, L., and Lampe, I.: Hemangioma of Vertebra Associated with Compression of the Cord, ibid. **47**:19-29 (Jan.) 1942. Frazier, C. H., and Spiller, W. G.: An Analysis of Fourteen Consecutive Cases of Spinal Cord Tumor, ibid. **8**:455-501 (Nov.) 1922. Frazier, C. H., and Alpers, B. J.: Meningeal Fibroblastomas of the Cerebrum: A Clinicopathologic Analysis of Seventy-Five Cases, ibid. **29**:935-989 (May) 1933. Friedman, E. D.: Lesion of the Upper Cervical Portion of the Cord, Resembling Combined System Disease: Presentation of a Case, ibid. **37**:430-435 (Feb.) 1937. Gardner, W. J.: Tumor of the Spinal Cord Associated with Bilateral Acoustic Tumors, ibid. **24**:1014-1022 (Nov.) 1930. Gill, J. C.: A Specimen of Tumor of the Brain, ibid. **20**:414-415 (Aug.) 1928. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme: A Primary Malignant Form of Brain Neoplasm; Its Clinical and Anatomic Features, ibid. **14**:139-191 (Aug.) 1925; Intraspinal Iodolography: Subarachnoid Injection of Iodized Oil as an Aid in the Detection and Localization of Lesions Compressing the Cord, ibid. **21**:1331-1386 (June) 1929. Globus, J. H., and Meltzer, T.: Metastatic Tumors of the Brain, ibid. **48**:163-226 (Aug.) 1942. Gould, E. M.: Tumors of the Posterior Cranial Fossa: Homolateral and Contralateral Pyramidal Tract Signs, ibid. **19**:509-514 (March) 1928. Grant, F. C.: The Successful Removal of Tumors of the Brain and of the Spinal Cord, ibid. **20**:634-638 (Sept.) 1928. Gross, S. W.: Cerebral Arteriography: Its Place in Neurologic Diagnosis, ibid. **46**:704-714 (Oct.) 1941. Hall, G. W., and Hirsch, E. F.: Paraplegia in Flexion, with Subacute, Combined Degeneration of the Cord, ibid. **23**:257-265 (Feb.) 1930. Helfand, M.: Status Pigmentatus: Its Pathology and Its Relation to Hallervorden-Spatz Disease, J. Nerv. & Ment. Dis. **81**:662-675, 1935. Horrax, G., and Bailey, P.: Pineal Pathology: Further Studies, Arch. Neurol. & Psychiat. **19**:394-414 (March) 1928. Kennedy, F.: Symptomatology of Frontal and Temporosphenoidal Tumors, J. A. M. A. **98**:864-866 (March 12) 1932. Kernohan, J. W., and Woltman, H. W.: Incisura of the Crus Due to Contralateral Brain Tumor, Arch. Neurol. & Psychiat. **21**:274-287 (Feb.) 1929. Keschner, M., and Davison, C.: Myelitic and Myelopathic Lesions: V. Compression of the Spinal Cord by Expanding Lesions Producing Mild, Moderate or Marked Interference with the Circulation Leading to Myelopathy, ibid. **30**:592-606 (Sept.) 1933. Lassek, A. M.: The Human Pyramidal Tract: IX. Effect of Paralysis Produced by Cerebral Tumors on Axons of Pyramids, ibid. **51**:213-215 (March) 1944. Naffziger, H. C., and Brown, H. A.: Hour-Glass Tumors of the Spine, ibid. **29**:561-584 (March) 1933. Ody, F.: Tumors of the Basal Ganglia, ibid. **27**:249-269 (Feb.) 1932. Pilcher, C.: Spongioblastoma Polare of the Pons: Clinicopathologic Study of Eleven Cases, ibid. **32**:1210-1229 (Dec.) 1934. Raeder, O. J.: Osteoma of the Spinal Arachnoid with Psammomatous Degeneration, ibid. **21**:1079-1086 (May) 1929. Sachs, E.; Rose, D. K., and Kaplan, A.: Tumor of the Filum Terminale, with Cystometric Studies: Report of Two Cases, ibid. **24**:1133-1153 (Dec.) 1930. Sands, I. J.: A Case of Pituitary Tumor with Coma Followed by Complete Recovery, ibid. **18**:461-462 (Sept.) 1927; Diagnosis and Management of Subarachnoid Hemorrhage, ibid. **46**:973-1005 (Dec.) 1941. Scarff, J. E.: Spastic Hemiplegia in an Infant Produced by a Congenital Cyst Entirely Replacing the Cerebellar Vermis, ibid. **31**:205 (Jan.) 1934. Schick, W.: Tumor High in the Cervical Region of the Spinal Cord Simulating Combined System Disease, ibid. **32**:1343-1345 (Dec.) 1934. Schlesinger, B.: Syndrome of the Fibrillary Astrocytomas of the Temporal Lobe, ibid. **29**:843-854 (April) 1933. Schnitker, M. T., and Ayer, D.: The Primary Melanomas of the Leptomeninges: A Clinicopathologic Study with a Review of the Literature and the Report of an Additional Case, J. Nerv. & Ment. Dis. **87**:45-73, 1938. Schwarz, G. A., and Rosner, A. A.: Displacement and Herniation of the Hippocampal Gyrus Through the Incisura Tentorii: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **46**:297-321 (Aug.) 1941. Sellheim, A. P.: Tumor of the Brain in the Monkey, J. belge de neurol. et de psychiat. **36**:240, 1936; abstracted, Arch. Neurol. & Psychiat. **38**:154 (July) 1937. Silverstein, A.: Cerebral Muscular Atrophy as a Significant Sign of Tumor of the Parietal Lobe with Presentation of Cases, ibid. **26**:670-674 (Sept.) 1931. Silverstein, A., and Winkelman, N. W.: A Case of Cerebellopontile Angle Tumor Showing Unusual Symptomatology: A New Operative Approach, ibid. **23**:838-841 (April) 1930. Spiller, W. G.: An Enchondroma of the Brain Removed with Recovery, ibid. **9**:536-538 (April) 1923. Stevenson, L., and Echlin, F.: Nature and Origin of Some Tumors of the Cerebellum: Medulloblastoma, ibid. **31**:93-109 (Jan.) 1934. Stone, L., and Menninger, W. C.: A Case of Psychosis Associated with Midline Cerebellar Tumors, ibid. **33**:399-405 (Feb.) 1935. Vincent, C.; Roger, H., and Giraud, M.: Olfactory Meningioma,

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of involvement of the pyramidal tract were selected for the following reasons: (1) because they had recovered from signs and symptoms referable to the pyramidal tract after surgical removal of the mass or after roentgen ray treatment or (2) because the tumor appeared to produce its effect although located at some distance from the known site of the pyramidal tract.

The pyramidal tract appears to be highly susceptible to effects of pressure, even of a slight degree. Extramedullary tumors which produced the Babinski signs have been removed from every part of the central nervous system, their removal being followed by loss of the reflex. These areas include the forepart of the frontal lobe and the parietal, occipital and temporal lobes, as well as the cavum septum pellucidi, the medulla oblongata, the cerebellum, the cerebellopontile angle, the filum terminale below the conus medullaris of the spinal cord and the pituitary and pineal glands. Most of the extramedullary tumors in this series were removed from the spinal cord. Speedy recovery was reported in some cases. Even in cases of long standing, when pressure is relieved there may be quick functional return of movements and disappearance of the Babinski sign. Apparently, few studies have been made on the correlation of pressure of the tumor on nerve tissue, destruction of the pyramidal tract and recovery. The indications thus far are that pressure on the cord in some cases causes local demyelination, without evidence of degeneration above or below the lesion. Obviously, more studies of this nature are needed before final conclusions can be formulated. For example, I have noted four different explanations as to why cerebellar lesions may cause a Babinski sign; they implicate respectively four parts of the central nervous system, namely, the cerebrum, the mesencephalon, the medulla oblongata and the upper part of the spinal cord. Each one of the explanations is not supported by scientific proof, as far as I have been able to determine.

Autopsy observations also support the view that remote tumor lesions can produce signs referable to the pyramidal tract. Here, again, tumors in every part of the nervous system, as well as extramedullary tumors, have been mentioned. Sometimes small tumorous lesions, remotely situated, may produce classic pyramidal signs, and various attempts to explain this phenomenon have been made. Edema, circulatory disturbance, anoxemia and increased intracranial pressure have been suggested in an attempt to clarify this occurrence. It may be mentioned that in some instances the pyramidal tract has appeared normal when studied post mortem.

One of the interesting features of the present study was the frequent occurrence of a bilateral Babinski sign with unilateral space-consuming lesions.

Inflammatory Processes.[9]—A variety of inflammatory processes may produce a transient

Rev. d'oto-neuro-opht. **9**:571, 1931; abstracted, Arch. Neurol. & Psychiat. **28**:197 (July) 1932. Warren, J. V., and Romano, J.: Spinal Epidural Granuloma: Report of a Case, ibid. **48**:789-798 (Nov.) 1942. Yaskin, J. C.: Homolateral Involvement of the Pyramidal Tract in Cerebral Tumors, ibid. **22**:1024-1028 (Nov.) 1929.

9. Alexander, M. E., and Allen, H. E.: Lethargic Encephalitis: A Report of Four Cases and an Analysis of One Hundred Cases Reported in the Literature, ibid. **3**:485-499 (May) 1920. Alfandary, I., and Stayitch, S.: Papillary Stasis in Encephalitis, Rev. d'oto-neuro-opht. **12**:503, 1934; abstracted, Arch. Neurol. & Psychiat. **33**:866-867 (April) 1935. Arnold, J. G.: Primary Ependymitis: Subacute Type with Occlusion of the Foramina of Monro and Hydrocephalus of the Lateral Ventricles, ibid. **32**:143-153 (July) 1934. Atkinson, M.: Localized Nonsuppurative Encephalitis Adjacent to a Focus of Infection in the Skull, ibid. **41**:556-564 (March) 1939. Beckmann, J. W.: Neurologic Aspects of the Epidemic of Encephalitis in St. Louis, ibid. **33**:732-751 (April) 1935. Bernstein, M.: The Hemiplegic Form of Epidemic Encephalitis: Report of a Case with Recovery, ibid. **13**:139-141 (Jan.) 1925. Brock, S., and Ivimey, M.: Toxic-Infectious Disease in the Peripheral and Central Nervous System—So-Called Neuronitis, ibid. **19**:129-141 (Jan.) 1928. Brouwer, B.: Arachnoiditis Adhesiva Circumscripta, ibid. **30**:639-644 (Sept.) 1933. Burr, C. W.: Typhoid Fever Apparent Exciting Cause of Cerebrospinal Symptoms of Syphilis, ibid. **14**:572-574 (Oct.) 1925. Cohen, I.: Justifications for and Results of Exploratory Laminectomy, ibid. **24**:373-380 (Aug.) 1930; Metastatic Abscess of the Brain: Operation; Recovery, ibid. **25**:910-912 (April) 1931. Courville, C. B., and Nielsen, J. M.: Otogenous Abscess of the Parietal Lobe, Bull. Los Angeles Neurol. Soc. **1**:65-70, 1936. Davidoff, L. M., and Dyke, C. G.: Series of Cases of Serous Meningitis, Arch. Neurol. & Psychiat. **36**:1376-1380 (Dec.) 1936. Davis, D. B., and Currier, F. P.: Forced Grasping and Groping, ibid. **26**:600-607 (Sept.) 1931. Davison, C., and Kelman, H.: Combined System Disease in Tabes Dorsalis, ibid. **38**:43-61 (July) 1937. Diamond, I. B., and Bassoe, P.: Abscess of the Brain: Report of Two Cases—One with the Clinical Picture of Epidemic Encephalitis and the Other with That of Tumor of the Brain, ibid. **19**:265-280 (Feb.) 1928. Gill, J. C., and Richter, R.: Encephalitis Disseminata: A Clinical and Anatomic Report of a Case with Features Akin to Multiple Sclerosis and Diffuse Sclerosis, ibid. **28**:1072-1090 (May) 1932. Gilpin, S. F.: A Patient with Myoclonus Following Epidemic Encephalitis, ibid. **5**:222-223 (Feb.) 1921; A Patient with Myelitis and Neuritis, ibid. **7**:142-143 (Jan.) 1922. Gorter, E.: Postvaccinal Encephalitis, J. A. M. A. **101**:1871-1874 (Dec. 9) 1933. Hassin, G. B.: Syphilis of the Oculomotor Nerve, Arch. Neurol. & Psychiat. **25**:116-127 (Jan.) 1931. Kaplan, A.: Abscess of the Brain: Recovery Following the Use of the Mosher Drain, ibid.

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Babinski sign, among which have been mentioned the following conditions: various forms of encephalitis (optic, nonsuppurative, serous, postvaccinal, disseminated, epidemic and lethargic encephalitis and acute benign meningoencephalitis), uveoparotid fever, otogenous abscess, epidemic parotitis, arachnoiditis adhesiva circumscripta, influenza, syphilis, tetanus, typhoid, radiculomyelitic syndrome, neuronitis, cerebellar abscess, abscess of the cord, myelitis complicating varicella, actinomycosis and myelitis. The terminology here used is that employed by the authors. In many cases the transient Babinski response and paralytic signs were followed by complete recovery. In some instances the investigators were unable to find any evidence of damage to the pyramidal tract at autopsy. The puzzling role of edema in manifestations of neurologic deficiencies has been discussed by some authors. Surgical drainage of abscess in this series has frequently been followed, sometimes rapidly, by disappearance of symptoms and signs referable to the pyramidal tract. One patient presented notable evidence of a transverse lesion of the cord, which was followed by recovery, including disappearance of the Babinski sign.

Miscellaneous Conditions.[10] — Other conditions reported in the literature as producing the

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33:667-673 (March) 1935. Kennedy, F.: Acute Benign Meningo-Encephalitis with Papilledema, ibid. **7**: 53-57 (Jan.) 1922; Acute Intracranial Edema Complicating Otitis Media, ibid. **27**:1497-1499 (June) 1932; Encephalomyelitis Optica: Report of a Case, ibid. **48**: 855-857 (Nov.) 1942. Keschner, M., and Sloane, P.: Encephalitic, Idiopathic and Arteriosclerotic Parkinsonism: A Clinicopathologic Study, ibid. **25**:1011-1041 (May) 1931. Klemmer, R. N.: A Case of Actinomycosis of the Cerebrum, ibid. **10**:479-480 (Oct.) 1923. Krabbe, K. H.: Varicella Myelitis, Brain **48**:535-539, 1925. Levin, P. M.: The Neurological Aspects of Uveoparotid Fever, J. Nerv. & Ment. Dis. **81**:176-191, 1935. McKaig, C. B., and Woltman, H. W.: Neurologic Complications of Epidemic Parotitis: Report of a Case of Parotitic Myelitis, Arch. Neurol. & Psychiat. **31**:794-808 (April) 1934. Nielsen, J. M.: Symptomatology of Otogenic Abscess of the Temporal Lobe, ibid. **29**:676-678 (March) 1933. Rabiner, A. M.: Radicular and Radiculomyelitic Syndromes with Recovery, ibid. **21**:224-226 (Jan.) 1929. Strauss, I., and Rabiner, A. M.: Myeloradiculitis: A Clinical Syndrome, with Report of Seven Cases, ibid. **23**:240-256 (Feb.) 1930. Woltmann, H. W., and Adson, A. W.: Abscess of the Spinal Cord: Report of a Case with Functional Recovery After Operation, Brain **49**:193-206, 1926. Zimmerman, H. M., and Yannet, H.: Nonsuppurative Encephalomyelitis Accompanying Chickenpox, Arch. Neurol. & Psychiat. **26**:322-332 (Aug.) 1931.

10. Abraham, A. E., and Baird, J. A.: Clinical and Subclinical Lead Intoxication, War Med. **2**:450-453 (May) 1942. Akelaitis, A. J. E., and Garvey, P. H.: Acute Demyelinizing Processes in the Nervous System, J. Nerv. & Ment. Dis. **94**:405-427, 1941. Alpers, B. J., and Dear, R. B.: Hemiatrophy of the Brain, ibid. **89**: 653-671, 1939. Arnheim, E. E.: A Case of Toxemia Presenting Unusual Clinical Manifestations, with Recovery, Arch. Neurol. & Psychiat. **16**:369 (Sept.) 1926. Babcock, C. G., and Brosin, H. W.: Hepatolenticular Degeneration: Report of a Case, ibid. **46**:431-439 (Sept.) 1941. Becker, F.: Triplegia Appearing Eighteen Years After an Injury of the Head and Greatly Benefited by Operation, ibid. **13**:660-661 (May) 1925. Benedek, L.: The Babinski Response in Eclampsia, Lancet **1**:1322, 1925. Bragman, L. J.: Reflexes in Amyotonia Congenita (Oppenheim): Report of a Case with Signs of Involvement of the Pyramidal Tract, Arch. Neurol. & Psychiat. **31**:161-163 (Jan.) 1934. Brock, S., and Wolf, A.: Cerebral Complications of Icterus Gravis Neonatorum, ibid. **36**:1368-1372 (Dec.) 1936. Bury, J. S.: The Significance of Some Early Symptoms of Nervous Disease, Lancet **2**:549-551, 1921. Cadwalader, W. B.: The Condition of a Patient in Good Health, but Exhibiting Automatic Movements of the Lower Limbs, Nineteen Years After Complete Transverse Section of the Spinal Cord by a Gunshot Wound, Arch. Neurol. & Psychiat. **4**:108-111 (July) 1920. Elliott, T. R., and Walshe, F. M. R.: The Babinski or Extensor Form of Plantar Response in Toxic States, Apart from Organic Disease of the Pyramidal Tract System, Lancet **1**:65-68, 1925. Frazier, C. H., and Ingham, S. D.: A Review of the Effects of Gunshot Wounds of the Head, Arch. Neurol. & Psychiat. **3**: 17-40 (Jan.) 1920. Freedom, L.: Cerebral Birth Palsies: A Contribution to Their Pathology with a Report of a Hitherto Undescribed Form, ibid. **26**:524-548 (Sept.) 1931. Furui, R.: The Pathology of Compression of the Spinal Cord, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **29**:169, 1927; abstracted, Arch. Neurol. & Psychiat. **19**:348-350 (Feb.) 1928. Goldensohn, L. N.; Clardy, E. R., and Levine, K.: Agenesis of the Corpus Callosum, J. Nerv. & Ment. Dis. **93**: 567-580, 1941. Goldstein, K., and Katz, S. E.: The Psychopathology of Pick's Disease, Arch. Neurol. & Psychiat. **38**:473-490 (Sept.) 1937. Gordon, A.: Familial Muscular Atrophy, ibid. **30**:460-462 (Aug.) 1933. Gordon, R. G., and Norman, R. M.: Further Observations on Neurological Abnormalities in Mental Defectives, J. Neurol. & Psychiat. **1**:173-179, 1938. Gurdjian, E. S., and Schlafer, N. H.: Fracture of the Skull with Injury of the Brain, Arch. Neurol. & Psychiat. **26**:583-592 (Sept.) 1931. Hassin, G. B.: Concussion of the Spinal Cord: A Case with the Clinical Picture of Amyotrophic Lateral Sclerosis, ibid. **10**:194-211 (Aug.) 1923. Hausman, L., and Bromberg, W.: Diabetic Exophthalmic Dysostosis, ibid. **21**:1402-1420 (June) 1929. Irish, C. W.: Presentation of a Case of Posttraumatic Psychosis with Mental Deterioration, ibid. **34**:1347-1349 (Dec.) 1935. Kasanin, J., and Crank, R. P.: A Case of Extensive Calcification in the Brain: Selective Calcification of the Finer Cerebral Blood Vessels, ibid. **34**:164-178 (July) 1935. Löwenberg, K.; Boyd, D. A., and Salon, D. D.: Occurrence of Pick's Disease in Early Adult Years, ibid. **41**:1004-1020 (May) 1939. Marcovitz, E., and Alpers, B. J.: The Central Nervous System in Mushroom Poisoning, ibid. **33**:53-71 (Jan.) 1935. Matthews, R., and McDade, R.: Neurologic Conditions in Three Hundred and Nine Mentally Defective Children, ibid. **29**:668 (March) 1933. Noica, D., and Radovici, A.: Abolition of the Babinski Sign by Cold and Its Reappearance After Heat, Rev. neurol. **26**:891, 1919; abstracted, Arch. Neurol. & Psychiat. **5**:330-331 (March) 1921. Parker, H. L., and Kernohan, J. W.: Stenosis of the Aqueduct of Sylvius, ibid. **29**:538-560

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Babinski sign are (1) hyperthermia, (2) cortical inferiority, (3) congenital or acquired atrophy, (4) unexplained demyelination, (5) cerebral calcification, (6) hepatolenticular degeneration, (7) Ascaris ova in the intestine, (8) hypercholemia, (9) uremia and (10) chronic masturbation. In 1 case the Babinski sign seemed to have a functional basis. The sign may be abolished by application of an Esmarch bandage on the leg, by a cold foot bath and by administration of physostigmine. A hot foot bath, as well as small quantities of scopolamine, elicits a latent Babinski sign. The position of the head on the body also modifies the reflex.

COMMENT [11]

For many years it has been thought that the sign of Babinski results only from destruction of the pyramidal tract. A permanent Babinski sign, according to this view, is produced only on complete loss of pyramidal fibers. The question arises as to why total disappearance of neurons is required to produce this lasting effect. Anatomically, it can mean only one thing, namely, that the axons which are destined for the first sacral segment, the part of the cord concerned with the Babinski reflex, must be scattered throughout the entire area of the pyramidal tract. If this is true, there is no localization of fibers within the tract. Further, the duration of the Babinski sign must be proportional to the amount of fiber loss. I am not sure that this thesis can be defended scientifically. Recovery, whether spontaneous or following surgical removal, and remote effects from space-consuming lesions are sometimes difficult to explain on this basis, especially in cases in which no diminution of pyramidal fibers is noted post mortem. With respect to the sign of Babinski, I believe that the effects of cortical ablations or experimental lesions in other portions of the central nervous systems in the chimpanzee or monkey cannot be compared or correlated too closely with the reflex which occurs in diseased conditions in man. Perhaps all the neurologic diseases which affect man cannot be simulated by application of the scalpel, cautery, suction apparatus or electrolytic instruments to the central nervous system of other primates. For example, whereas it required widespread cortical damage in the monkey (hemidecortication and ablation of the thalamus) to produce the sign of Babinski, the reflex was easily elicited in a monkey with a tumor confined to the occipital lobe.

On analysis of about 1,000 cases the actual and circumstantial evidence appears to be overwhelming that the sign of Babinski can be exhibited without any fibers of the pyramidal tract being destroyed. Cases in which this occurred formed a fairly high percentage of the total number studied, and they may, therefore, be of sufficient importance to be taken seriously in the diagnosis of neurologic diseases.

(March) 1933; Parenchymatous Cortical Cellebellar Atrophy (Subacute Cerebellar Encephalitis), ibid. **33**: 959-975 (May) 1935. Patrick, H. T.: The Symptoms of Lhermitte in Multiple Sclerosis, ibid. **23**:1075-1077 (May) 1930. Patten, C. A.: Cerebral Birth Conditions, with Special Reference to Cerebral Diplegia, ibid. **25**: 453-468 (March) 1931. Riley, H. A., and Brock, S.: Rhythmic Myoclonus of the Muscles of the Palate, Pharynx, Larynx and Other Regions: A Clinical Report of Three Cases, ibid. **29**:726-741 (April) 1933. Shearer, C.: A Case of Functional Epileptiform Seizure with Babinski Reflex, Lancet **1**:1322, 1925. Strecker, E. A.; Taft, A. E., and Willey, G. F.: Mental Sequelae of Carbon Monoxide Poisoning, with Reports of Autopsy in Two Cases, Arch. Neurol. & Psychiat. **17**:552-554 (April) 1927. Thomas, J. J.: Report of a Case of Cervical Syringomyelia, ibid. **6**: 98-99 (July) 1921. Verhaart, W. J. C.: An Unclassified Degenerative Disease of the Central Nervous System, ibid. **44**:1262-1270 (Dec.) 1940. Waggoner, R. W.; Löwenberg, K., and Speicher, K. G.: Hereditary Cerebellar Ataxia, ibid. **39**:570-586 (March) 1938. Yaskin, J. C.: Injury of One Pyramidal Tract Resulting from a Knitting Needle Puncture Wound of the Cervical Region of the Cord, ibid. **9**:413-414 (March) 1923. Yaskin, J. C., and Wilson, G.: Case of Traumatic Psychosis in a Child, ibid. **37**:201-205 (Feb.) 1937.

11. Cobb, S.: Causes of Epilepsy, Arch. Neurol. & Psychiat. **27**:1245-1263 (May) 1932. Dandy, W. E.: The Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 12, chap. 1. Filimonoff, I. N.: Nature of the So-Called Pathologic Reflexes, Ztschr. f. d. ges. Neurol. u. Psychiat. **103**:416-434, 1926. Forster, F. M., and Campbell, J. B.: The Sign of Babinski in Macaca Mulata, J. Nerv. & Ment. Dis. **96**:493-498, 1942. Fulton, J. F., and Viets, H. R.: Upper Motor Neuron Lesions: Analysis of Syndromes of Motor and Premotor Areas, J. A. M. A. **104**:357-362 (Feb. 2) 1935. Goldflam, S.: Die diagnostische Bedeutung des Rossolimoschen Reflex bei Erkrankungen des Zentralnervensystems: Eine klinischanatomische Studie, Berlin, S. Karger, 1930, p. 274. Goldstein, K.: The Sign of Babinski, J. Nerv. & Ment. Dis. **93**:281-296 (March) 1941. Keschner, M., and Grossman, M.: Cerebellar Symptomatology Evaluation on the Basis of Intracerebellar and Extracerebellar Lesions, Arch. Neurol. & Psychiat. **19**:78-94 (Jan.) 1928. Langworthy, O. R.; Highberger, E., and Foster, R.: Hemiplegia with the Leg in Flexion, ibid. **34**: 520-532 (Sept.) 1935. Orton, S.: A Theory of the Genesis of Tremor in Lenticular Disease, ibid. **23**:183-187 (Jan.) 1930. Spiller, W. G.: Hyperreflexia of Lower Limbs After Exercise, J. A. M. A. **87**:639-640 (Aug. 28) 1926. Tournay, A.: The Babinski Sign: Its Characteristics, Mechanism and Significance, Arch. Neurol. & Psychiat. **17**:834-835 (June) 1927. Zador, J.: Conditions Affecting the Pathogenesis of the Babinski Reflex, Monatschr. f. Psychiat. u. Neurol. **64**:336-349, 1927; abstracted, Arch. Neurol. & Psychiat. **20**: 847-848 (Oct.) 1928.

It is difficult to find a common denominator to explain the production of a Babinski sign in cases without loss of fibers in the pyramids. If the pyramidal tract is concerned at all in the pathogenesis of this neurologic sign, then there are certain factors or phenomena which constantly appear in many cases, such as anoxemia, pressure, circulatory disturbance, edema, augmented cerebrospinal pressure and constitutional weakness of the pyramidal neurons. It is logical to assume that physiologic block of impulses mediated by the pyramidal tract would have the same effect on the lower motor neuron as does loss of fibers. The question therefore arises as to whether any of the phenomena of neurologic disease mentioned can produce a physiologic block of impulses conducted by the pyramidal tract. Any analysis must consider the pyramidal neuron from its beginning to its termination because it apparently is vulnerable throughout its entire extent.

Probably the most defensible explanation of a possible physiologic block of pyramidal conduction is that embodied in the broad term "depression of nerve activity." Any one of the phenomena mentioned, i. e., anoxemia, pressure edema, circulatory disturbance or increased intracranial pressure, might conceivably have a depressant effect on the pyramidal tract fibers. The various drugs mentioned are described, for the most part, as having an inhibitory effect on the cortical cells. There may be cortical inhibition during sleep, in narcoleptic and cataleptic attacks and on physical exertion, all of which have been accompanied by signs of involvement of the pyramidal tract without destruction. Anoxmeia, whether it is caused by hypoglycemia, loss of blood, temporary circulatory arrest, air embolism, polycythemia, oligocythemia, an oversensitive carotid sinus reflex, Cheyne-Stokes respiration, carbon monoxide poisoning or other factors, may cause a depression of nerve activity in the pyramidal tract.

Pressure of space-consuming lesions on the pyramidal tract might easily block descending nerve impulses. Some unusual cases of motor recovery are reported in the literature when such a mass has been removed by operation or controlled by roentgen irradiation. The few clinicopathologic investigations that have been made in this respect indicate that the pathologic changes consist largely of local demyelination without descending or ascending degeneration. Such observations are consistent with the speedy recoveries reported. On the other hand, one report states that in general the pathologic changes were in agreement with the clinical symptoms. Many observers have been at a loss to describe the remote or the neighborhood effects of certain lesions, especially tumors. In cases of such lesions, spreading edema or circulatory disturbance is described repeatedly, and in some instances the pyramidal tract has appeared normal at autopsy. On the basis of this study, it is difficult to neglect edema as a causative factor in the production of a Babinski sign. The pressure of tumors or other space-consuming lesions on blood vessels might create a partial anoxemic condition in the areas surrounding the tumor mass. It is interesting that lobotomy and anterior chordotomy, involving narrow incisions made at some distance from the known region of the pyramidal tracts, may cause a transient Babinski sign. Edema probably best explains this reaction.

Inflammation, through the elimination of toxins by bacteria, might conceivably exert a depressant effect on the nerve cells or the fibers constituting the pyramidal tract. The toxins which may be prevalent in cases of the hepatic insufficiencies, uremia, Ascaris infestation of the intestine and the unexplained myelitic processes may be placed in this category.

The role of some miscellaneous conditions which produce the Babinski sign is difficult to explain. Among these conditions may be mentioned hyperthermia, cortical inferiority, congenital atrophy and masturbation. Cortical inferiority is probably the easiest of these factors to discuss. There must be great individual variation in the stability of the pyramidal tract, since it certainly is not cast in any standard mold. Persons with a relatively weak pyramidal system and with poor power of transmission might exhibit the Babinski sign, whereas persons with a more durable system would not. Studies on apparently young normal persons and on mentally defective and epileptic subjects indicate that this may be true. I cannot offer any suggestions as to why the Babinski sign should be associated with chronic masturbation. Further observations are undoubtedly necessary. The 1 case cited in which the Babinski sign appeared to be due to a functional disturbance should probably not be accepted without further confirmation; an overwhelming mass of evidence is against the elicitation of a Babinski sign on a functional or a hysterical basis.

That the Babinski sign may be modified in a number of ways suggests that the integrity of the peripheral nerves is important. An Esmarch bandage on the leg abolishes the reflex, and the position of the head on the body has altered the sign in the hands of some observers. Hot foot

baths tend to bring out a latent Babinski sign, whereas cold water has the opposite effect. Scopolamine in minute quantities brings out a latent Babinski sign and with administration of larger amounts a Babinski sign can be elicited in normal persons; physostigmine has the opposite effect.

An interesting feature noted in the study was the frequent occurrence of a bilateral Babinski sign with a unilateral lesion. This was especially true of space-consuming masses in the cerebrum. It is realized that this phenomenon has been explained in a few instances by the shifting of the brain mass so that the opposite cerebral peduncle comes in contact with the tentorium cerebelli. Shifting of the pyramids of the medulla against the border of the foramen magnum has also been mentioned as a possible explanation for the phenomenon. Although this explanation may suffice in some cases, I feel that it may not be the only one and that further investigation is in order. In order to determine the cause of a bilateral Babinski effect in such cases, one must first be sure of all the factors involving production of the reflex on one side.

I wish to emphasize that it is not intended to imply that the conditions which have been enumerated and discussed in this article always produce a Babinski sign with paralytic symptoms. The cases in this series are selected; they were chosen because in some manner they gave evidence against the view that the Babinski sign and destruction of the pyramidal tract go hand in hand. Further search would unquestionably bring to light many additional pertinent cases, perhaps thousands, in support of the essential observations reported here. A monograph, at least, could be written on the subject if the evidence were comprehensively reviewed.

CONCLUSIONS

1. The evidence appears to be overwhelming that the sign of Babinski can be elicited in persons with no loss of pyramidal tract fibers.

2. A small percentage of persons without any manifestations of neurologic disease may exhibit the Babinski sign on proper stimulation.

3. A temporary sign of Babinski can be produced in normal subjects under various conditions, as follows: (a) severe exertion; (b) subjection to the action of depressant drugs; (c) spontaneous or induced hypoglycemia; (d) deep sleep; (e) blood disorders; (f) ingestion of certain toxic chemicals or poisonous gases, and (g) many miscellaneous conditions.

4. Many systemic or neurologic inflammatory diseases may cause a transient or fluctuating Babinski sign.

5. Pressure on the pyramidal tract almost invariably produces an extensor toe response, which may disappear when the cause of the pressure is removed. In some of the cases in this series no signs of descending degeneration in the pyramidal tract were apparent at autopsy.

6. Remote space-consuming lesions may produce a sign of Babinski through edema, anoxemia or other phenomena.

7. The mechanism involved in producing the sign of Babinski in disease conditions in man may be of a capricious nature.

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SYNCHRONIZATION OF SPONTANEOUS ACTIVITY IN DENERVATED HUMAN MUSCLE

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If mammalian muscle is deprived of its nerve supply, no spontaneous activity can be observed for several days. After that period spontaneous contraction of individual muscle fibers sets in, and may persist for a year or longer unless nerve regeneration occurs or the contractile muscle tissue disappears.[1] This activity is not visible through the skin. Visible movements of groups of muscle fibers are always associated with the discharge of at least one motor nerve impulse.[2] To our knowledge, there has not been described in the literature a case of spontaneous synchronized activity of muscle fibers in a completely denervated muscle. Such a case, in which absence of innervation could be ascertained by various methods, has been under observation for several months at an Army general hospital.

REPORT OF A CASE

Clinical History.—A white man aged 24 entered the hospital Sept. 10, 1943, because of paralysis of the left ulnar nerve. He had been in an automobile accident in November 1940, at which time a small splinter of glass entered the medial surface of the left arm just above the elbow. The wound healed quickly, and he had no symptoms referable to the ulnar nerve. In April 1941 he noticed the onset of weakness of the left hand and diminution of sensation in the area supplied by the ulnar nerve. In June 1943, on admission to another general hospital for a minor ailment, he was found to have almost complete paralysis of the left ulnar nerve. It was noted that all the muscles supplied by this nerve showed some response when tested with faradic and galvanic currents. On July 19 the ulnar nerve was explored above the elbow. At a point about 0.5 cm. from the epicondyle there was a firm nodule, 0.75 cm. in diameter, which involved the entire nerve trunk. This nodule was excised, together with 2 to 3 mm. of normal-appearing nerve tissue on either side of the mass. The severed ends of the completely interrupted nerve were then approximated and sutured. On microscopic examination the nodule showed interlacing bundles of nerve fibers, and a pathologic diagnosis of neuroma was made.

Examination at the time of admission to this hospital, on September 10, showed no abnormalities except those associated with the left ulnar nerve. There was pronounced atrophy of the interosseus and lumbricalis muscles but much less conspicuous wasting of the muscles of the hypothenar eminence. Sensation was completely absent over the distribution of the ulnar nerve. There was no voluntary motor activity in any of the muscles innervated by this nerve. The fourth and fifth fingers were continually in a position of firm flexion but could be straightened without difficulty on passive movement. Numerous spontaneous movements over the hypothenar eminence were easily visible. They appeared to be due to the synchronous activity of large groups of muscle fibers, having the appearance of the spontaneous fasciculations seen in degenerative disease of the lower motor neuron or after the administration of neostigmine. No such spontaneous movements were seen in any other region. During the three months in which the patient was observed each day there was a gradual and progressive decrease in the number of these spontaneous movements. However, a momentary increase in their rate could be effected by putting the muscles on a stretch. These abnormal movements had not been noted during his stay in the other hospital. The time of their onset could not be accurately determined, but they were present on admission to this general hospital.

Method.—To obtain an accurate picture of the activity, electrical recordings were made from abductor digiti quinti and other muscles of the hypothenar eminence, with the method of Harvey and Masland (1941).[3] In certain observations the potentials were led to the input of a condenser-coupled amplifier and recorded on a cathode ray oscillograph. In others, when continuous recording was necessary, a General Electric–Victor electrocardiograph was used. The motor nerve was stimulated by means of condenser discharges from gas discharge tube circuits, led through a specially shielded and balanced transformer.

Results.—The general pattern of spontaneous muscle activity could be recorded on an electrocardiograph (figure, *B*). The frequency of discharge was usually 8 to 10 per second, but at times it was lower. Simultaneously fine muscle movements could be observed through the skin. A more detailed picture of the individual discharges was seen in the records taken on a cathode ray oscillograph, as shown in *A* of the figure. The potentials in this record represent either the same

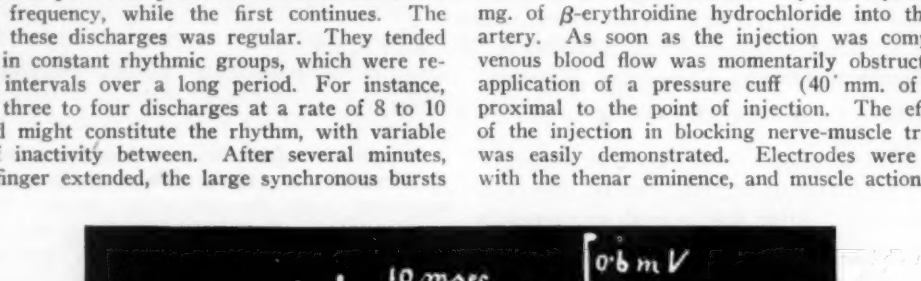
1. Tower, S. S.: The Reaction of Muscle to Denervation, Physiol. Rev. **19**:1, 1939.

2. Denny-Brown, D. E., and Pennybacker, J.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311, 1938.

3. Harvey, A. M., and Masland, R. L.: Method for Study of Neuromuscular Transmission in Human Subjects, Bull. Johns Hopkins Hosp. **68**:81, 1941.

or closely adjacent groups of muscle fibers discharging repetitively.

An increase in the number of spontaneous muscle movements could always be produced by extension of the fingers. In *C* of the figure some of these synchronous contractions were recorded from the abductor digiti quinti muscle after stretch of the fifth finger. In this tracing one group of muscle fibers is seen to discharge at a rate of 8 to 10 per second; soon a much larger wave of potentials passes the electrodes at about the same frequency, while the first continues. The pattern of these discharges was regular. They tended to appear in constant rhythmic groups, which were repeated at intervals over a long period. For instance, groups of three to four discharges at a rate of 8 to 10 per second might constitute the rhythm, with variable periods of inactivity between. After several minutes, with the finger extended, the large synchronous bursts disappeared gradually, and the muscle returned slowly to the level of activity which existed before the stretch. Apparently, accommodation to the stretch stimulus occurred.



A and *B*, muscle action potentials of spontaneous activity recorded from abductor digiti quinti muscle. *A* shows potentials recorded with a cathode ray oscillograph, and *B*, activity recorded on the slowly moving film of an electrocardiograph. *C*, muscle activity recorded on an electrocardiograph from the abductor digiti quinti muscle after stretch of the fifth finger.

The important feature of these muscle movements was their appearance in muscles which had no apparent innervation. Although the nerve which supplied these muscles had been completely divided at operation, and no voluntary movement was evident, it seemed necessary to obtain additional proof that these unusual synchronized movements were initiated in muscle fibers which were deprived of any functioning nerve fibers.

It was first necessary to exclude the possibility of innervation by fibers from another nerve. The median, radial and ulnar nerves of the normal arm were stimulated electrically and the action potentials recorded from appropriate areas. The strength of the stimulus necessary to produce a maximal response of the muscle to both single and repetitive nerve impulses was determined. With stimuli the strength of which was at least 30 per cent greater than this, the corresponding nerves were stimulated on the involved side with the recording electrodes placed over the muscles which were the seat of the spontaneous activity. In no instance was there any detectable response after stimulation of the motor nerve, although the amplification used was sufficient to record with ease the spontaneous discharges.

As an additional means of excluding nerve discharges as the basis of these synchronized movements, the muscles were "curarized" by the injection of 200 mg. of β-erythroidine hydrochloride into the brachial artery. As soon as the injection was completed, the venous blood flow was momentarily obstructed by the application of a pressure cuff (40 mm. of mercury) proximal to the point of injection. The effectiveness of the injection in blocking nerve-muscle transmission was easily demonstrated. Electrodes were connected with the thenar eminence, and muscle action potentials characteristic of voluntary movements of the thumb were recorded prior to the injection. For four to five minutes after the injection voluntary movement of the thumb was not possible, and during that time no action potentials could be recorded from the thenar eminence.

However, the spontaneous discharges from the muscles of the hypothenar eminence persisted with the same frequency and showed the usual increase in number when the muscles were stretched. It seems clear from these observations that the responses arose in muscle fibers which had been deprived of any motor innervation.

The grouping and rhythmicity of these discharges were similar to those described by Adrian and Gelfan[4] in frog muscle in the presence of a deficiency of calcium following the application of sodium citrate. One gram of calcium gluconate was given intravenously, and the contractions were recorded electrically before and after

4. Adrian, E. D., and Gelfan, S.: Rhythmic Activity in Skeletal Muscle Fibers, J. Physiol. **78**:271, 1933.

the injection. No change could be detected in the frequency or size of the movements, or in the increased number of discharges following stretch.

It seemed of importance to determine the effect of neostigmine on these spontaneous twitchings, particularly as the possibility existed that acetylcholine might be concerned in the mechanism of their production. One milligram of neostigmine methylsulfate was injected into the brachial artery, and the venous return was occluded for one minute. The muscles innervated by the median and radial nerves became weak and within a short time were the seat of numerous spontaneous fasciculations. Voluntary strength gradually returned during the next ten to fifteen minutes, and the fasciculations persisted for thirty to forty minutes, as described in normal subjects by Harvey and Lilienthal.[5] In addition, there was a more general effect, with spontaneous twitchings in the tongue and the orbicularis muscle group. Continuous electrical recordings of the responses from the hypothenar group showed no detectable change in the type and degree of the spontaneous discharges during the thirty minutes following the injection.

COMMENT

From the observations which have been described it is clear that the spontaneous activity had its origin in denervated muscle. Furthermore, the action potentials produced demonstrated that the activity resulted from the synchronous discharge of groups of muscle fibers. Once such a discharge originated in a given area of the muscle it usually continued for many minutes with a definite rhythm. After stretch the activity was enhanced, and spontaneous impulses sometimes originated from several foci, each with its independent rhythm.

It is of interest that in each experiment the action potential spikes always passed the recording electrodes from the same direction, as determined by their polarity. This evidence is not conclusive but indicates that a comparatively small area possessed certain properties not found in other portions of the muscle and was able to give rise to these spontaneous discharges and to synchronize their activity.

Spontaneous synchronized discharges have been described during block in neuromuscular transmission and in denervated muscle of frogs in the presence of a deficiency of calcium.[6] It has also been demonstrated by one of us (S. W. K.)[7] that such discharges set up by a reduction of calcium ions during a period of neuromuscular block originate at the motor end plates.

There is evidence from other sources that activity can originate spontaneously at the end plate region. In the denervated diaphragm of the rat, fibrillary activity was shown by Hayes and Woolsey[8] to have its origin at the junctional regions. Forty to ninety days after motor denervation of frog muscle, bursts of impulses may arise at the end plates, particularly after stretch or mechanical stimulation, and continue for several minutes. Also, in cases of tetany fibrillary activity has been shown to originate at the end plates.[9]

Although it cannot be demonstrated conclusively, it is suggestive that the spontaneous activity in the present case may have originated in the region of the motor end plates. Such activity may be of more frequent occurrence than is realized, and with further observation more may be learned of its nature. It was not possible to determine whether this synchronous activity was coexistent with fibrillation in other muscle fibers, but it seems reasonable to assume that it had its origin in the same area of the muscle as this type of activity, which is uniformly present in denervated striated muscle. The rate of the spontaneous discharges in the present case was similar to that noted by other authors in fibrillating muscle fibers (Tower,[1] page 9). It is felt that the spontaneous activity in this case was nothing more than synchronized fibrillation.

SUMMARY

In an investigation of the spontaneous synchronized activity of groups of muscle fibers in muscles of the hypothenar eminence of a patient in whom the motor fibers of the ulnar nerve had been completely interrupted for four months, the following observations were made:

1. Electromyographic recordings showed muscle groups discharging at a frequency of 8 to 10 per second. The discharges tended to appear in constant rhythmic groups. The number of spontaneous movements could be greatly increased by stretching of the muscles.

2. Complete absence of innervation of the active muscles was demonstrated by various methods.

3. The origin and the synchronization of the activity may have occurred at the region of end plates in the denervated muscles.

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5. Harvey, A. M., and Lilienthal, J. L.: Observations on Nature of Myasthenia Gravis: Intra-Arterial Injection of Acetylcholine, Prostigmine and Adrenaline, Bull. Johns Hopkins Hosp. **69**:566, 1941.

6. Kuffler, S. W.: Specific Excitability of the End-plate Region in Normal and Denervated Muscle, J. Neurophysiol. **6**:99, 1943.

7. Kuffler, S. W.: The Effect of Calcium on the Neuromuscular Junction, J. Neurophysiol. **7**:17, 1944.

8. Hayes, G. J., and Woolsey, C. N.: The Unit of Fibrillary Activity and the Site of Origin of Fibrillary Contractions in Denervated Striated Muscle, Federation Proc. **1**:38, 1942.

9. Kuffler, S. W.: Excitability Changes at the Nerve-Muscle Junction During Tetany, to be published.

ELECTRIC CONVULSIVE THERAPY OF THE PSYCHONEUROSES

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The simplicity of electric convulsive therapy and its possible application to ambulatory patients seem to favor its indiscriminate use in treatment of all types of psychoneuroses. This possibility suggested a broader clinical investigation for the purpose of determining the actual value of this method for the neuroses. Another reason for such a therapeutic study was the expectation that a comparison of reactions in the neuroses and those in the major psychoses might contribute to a better understanding of the effect of shock treatment in general. The difference between the effect of electric convulsive therapy and that of other organic methods applied in treatment of the neuroses promised to offer further points of interest.

Cerletti,[1] the originator of electric convulsion therapy was the first to try the method in a few cases of severe psychoneuroses, without more than transient results, which he attributed to autosuggestion. Many experienced investigators reported discouraging results, or even warned against the use of the method with neurotic patients. Others[2] recommended it, and a compilation from the entire literature revealed a rather high incidence of improvement.[3]

Our material consists of 65 patients whose illness was severe enough to cause them to seek voluntary admission to the New York State Psychiatric Institute; many of them had been under observation for several months before being subjected to electric convulsive therapy. This period of observation permitted us not only to reduce the number of diagnostic errors but to exclude improvements due to change from the home environment and to the psychotherapeutic approach. Most of these patients had had psychotherapy prior to shock treatments and remained under the care of the psychotherapeutist during the convulsion therapy.

Results of Electric Convulsion Therapy in Sixty-Five Psychoneurotic Patients

Type of Psychoneurosis	Total No. of Patients	Immediate Results: Great Improvement	Immediate Results: Slight Improvement	Immediate Results: No Improvement	Later Development: Great Improvement	Later Development: Slight Improvement	Later Development: No Improvement	Outcome Unknown
Obsessive-compulsive	16	5 (31.3%)	9 (56.2%)	2 (12.5%)	5 (35.7%)	4 (28.6%)	5 (35.7%)	2
Anxiety hysteria	15	2 (13.3%)	3 (20%)	10 (66.7%)	2 (14.3%)	1 (7.1%)	11 (78.6%)	1
Conversion hysteria	13	5 (38.5%)	2 (15.4%)	6 (46.1%)	2 (22.2%)	2 (22.2%)	5 (55.6%)	4
Mixed psychoneurosis	10	2 (20%)	4 (40%)	4 (40%)	1 (11.1%)	2 (22.2%)	6 (66.7%)	1
Reactive depression	11	10 (99.1%)	1 (0.9%)	..	7 (77.8%)	2 (22.2%)	..	2
Total	65	24 (36.9%)	19 (29.3%)	22 (33.8%)	17 (31%)	11 (20%)	27 (49%)	10

The accompanying table shows the results for patients with various types of psychoneuroses. A classification was chosen which, it was hoped, would facilitate control investigations, alhtough it was realized that pure forms of psychoneuroses are rare and that a subtype can refer only to the predominant symptom presented by the individual patient. The table is offered as a basis for the discussion, but more importance is attributed to conclusions from our clinical observations.

The results with the various subtypes of the psychoneuroses will be discussed separately because they differ from each other in kind and in degree. The incidence of improvement in the whole group of 65 patients is of no interest because figures based on

From the New York State Psychiatric Institute and Hospital.

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1. Cerletti, U.: Electro-Shock, Riv. sper. di freniat. **64**:209, 1940.

2. Moriarty, J. D., and Weil, A. A.: Combined Convulsive Therapy and Psychotherapy of the Neuroses, Arch. Neurol. & Psychiat. **50**:685 (Dec.) 1943.

3. Impastato, D. J., and Almansi, R. J.: A Study of Over Two Thousand Cases of Electrofit-Treated Patients, New York State J. Med. **43**:21, 1943.

mixed material depend entirely on the ratio between the number of patients with a favorable and the number with an unfavorable prognosis.

RESULTS

Obsessive-Compulsive Neuroses. — The reaction of patients with this condition showed certain features in common: The sudden, dramatic improvement after three or four treatments, so common in psychotic patients, was not observed. However, there was frequently a gradual change after six, eight or more convulsions. At this point, the patient still retained his obsessive-compulsive symptoms, but his emotional response to them was lessened. They did not bother him so much, and he felt more at ease. When therapy was continued for twenty sessions, the patient who became deeply confused sometimes lost all recollection of his compulsions or obsessions. But closer observation revealed that this loss was only part of a farther-reaching amnestic syndrome, which was not limited to forgetting of his symptoms. It soon became obvious that the "recovery" from his obsessions and compulsions was a sham one. Discontinuation of treatment in most instances led to reappearance of the obsessive-compulsive symptoms in one or two weeks, that is, when the mental symptoms of organic origin had disappeared.

A small number of patients benefited more lastingly from the treatment. Even though the symptoms returned, they were accepted by the patient as something of less importance which did not interfere greatly with his activities. It is at this time that psychotherapy has its best chances. The patient, who is far more accessible, may be helped to become interested in his personal and professional life and enabled to take up his activities outside the hospital. Such occasional results justify an attempt to treat certain patients with a severe obsessive-compulsive neurosis which could not be influenced otherwise. A few surprising results in this group suggested a possible relation of the disorder to the psychoses.

Anxiety Hysteria.—Anxiety is probably the most frequent symptom encountered in neurotic patients, and it is also the symptom least amenable to electric convulsive therapy. Some patients may become temporarily relaxed, less tense and thus more accessible to psychotherapy. As a whole, however, patients with anxiety hysteria benefited least from the treatment. The condition of most of the patients remained unimproved during the entire course of treatment; some became worse or were frightened by the treatment. The few who improved slightly under treatment had a relapse after a short time.

Conversion Hysteria.—The results of treatment of conversion hysteria were almost as unsatisfactory. The hysterical character cannot be influenced and is a hazardous factor in the patient's reaction to the treatment. Hysterical symptoms may occasionally be effected, as with every method, but new symptoms may be brought out by the treatment. Improvement, such as that of a patient with hysterical paralysis, was strikingly reminiscent of the suggestive influence of faradic and other nonconvulsive electric treatments, as used formerly in the management of gross manifestations of hysteria. When we state this, we wish to make it clear that by no means do we agree with those who explain all improvement occurring during shock therapy by suggestion or by the terrifying effect reminiscent of methods applied in treatment of the psychoses centuries ago.

It should be noted that it is particularly the patients with conversion hysteria who complain of being made worse. Muscular pain, frequent in all patients receiving electric convulsive treatment, is often attributed to the heart or to other organs. Some patients elaborated on the experience of dizziness or other sensations during the period of awakening or were terror stricken by the amnesia. One patient reacted with a Ganser syndrome of short duration after only two treatments. The patients who showed improvement were chiefly those who, impressed by recovery in others, had requested shock therapy or those in whom the conversion syndrome was accompanied by a strong depressive element.

Psychoneurotic Depressions.—The best results were observed in treatment of the so-called psychoneurotic depressions. Like manic-depressive and involutional depressions, the depressions of neurotic patients had a remission after approximately four treatments, although the neurotic setup remained unchanged. It depended on the seriousness of the patient's neurotic attitude whether or not his readjustment succeeded. Some of the patients received a strong stimulus from the euphoric reaction which often followed the treatment. Failure is illustrated by the case of a physician who, suffering from a psychoneurosis of long standing, had gone into a depression. When cured of his depression, his energy returned but fizzled out in unproductive activities, and his neurotic attitude prevented him from returning to work. However, the majority in this group benefited from the treatment. The shock treatments should be followed by psychotherapy, which with other types of depressions was found to be a desirable, but not in-

dispensable condition for the production of remissions with electric convulsive therapy.

Mixed Psychoneuroses.—Although most psychoneuroses are of "mixed" type, only a small group of patients had to be classified under this head because no well defined symptoms predominated. Nothing need be added to the observations made on the patients in the other groups. We may mention here the experiences of other authors with certain ill defined forms of neurosis. Myerson [4] noted good results in cases of a chronic neurosis which he described as an "anhedonic state." Favorable results were likewise reported by Kennedy and Wiesel [5] in patients with a so-called manic-depressive equivalent, persons with episodes of somatic complaints and only moderate depression.

COMMENT

The subjective reaction of the patient to the experience of the treatment should be commented on. What some patients describe as "feeling at ease as never before" is complained of by others as "losing control of myself." Complaints are manifold. One patient said that he could not see as clearly as before the treatment, but he added, "It might not be so much my eyesight as my mind." After a greater number of treatments the patients become indifferent. One who had relapsed commented: "During the treatment I felt just swell; I was in a fog, and therefore nothing bothered me." The opinion has been expressed that neurotic patients show more severe memory defects than psychotic patients. Closer observation reveals that it is only the reaction to this impairment which is felt more intensely by neurotic patients. One patient refused treatment because he was afraid that owing to his impairment of memory the physicians would make him think what they wished and that he would lose control of the situation. Others were afraid of becoming insane. At a time when tests already showed the disappearance of all traces of memory defect, the neurotic patient might still hold the treatment responsible for any difficulty he might have in remembering things.

Before we proceed to a final evaluation of our results with this treatment, attempts to treat psychoneurotic patients by other organic methods should be discussed. Insulin shock therapy has been used little with neurotic patients. A favorable influence, especially with patients suffering from anxiety neuroses, has frequently been reported. Since metrazol, like the electric current, is a convulsive agent, comparison of the results with these two agents is of greater interest. Shapiro and Freeman [6] reported good results with metrazol; in their experience improvement usually did not appear before at least a slight confusional state was reached. They took exception to the theory that fear is the therapeutic agent. Other authors have stressed the importance of the anxiety between the time of injection and the appearance of a convulsion for the successful treatment of psychogenic symptoms. This might explain the apparent superiority of metrazol over electric convulsive therapy in certain cases of acute neurotic reactions, e. g., war neuroses.

The best results of an organic treatment of neurotic patients were described by Freeman and Watts,[7] with frontal lobotomy. This operation and electric convulsive therapy have in common the organic interference with cerebral functions, which, however, is transitory in the case of convulsive treatment, but permanent, and therefore of more lasting therapeutic effect, in the case of frontal lobotomy. Psychosurgery and electric convulsive therapy produce "blanching of the emotional coloring connected with obsessive ideas," relief of tension and certain unpleasant organic side effects, such as unrestrained behavior and impaired judgment. But both the side effects and the improvement are of short duration with electric convulsive therapy. The superiority of the operative procedure is illustrated by 1 of our cases.

F. A., a man aged 32, since 1939 had suffered from the obsession of not being able to breathe. He had to watch his respiration every moment and was unable to concentrate on anything else. In 1942 he applied for voluntary admission to the Pilgrim State Hospital, where he received twenty electric convulsive treatments. After ten treatments the obsessive idea had lost its importance for him; after sixteen treatments it had disappeared completely, but this was only part of a Korsakoff-like syndrome. Ten days after the last treatment the obsession returned, and six weeks after the end of therapy the patient suffered as much as before. Ten months later a frontal lobotomy was performed by Dr. T. J. Putnam, with full success. The patient has now been under the observation of the New York State Psychiatric Institute for five months since the operation. He lost his obsessions

4. Myerson, A.: Further Experience with Electric Shock Therapy in Mental Diseases, New England J. Med. **227**:403, 1942.

5. Kennedy, F., and Wiesel, B.: A Report on the Results of Electric Shock Treatment on Mental and Emotional Symptoms, New York State J. Med. **42**: 1663, 1942.

6. Shapiro, H. D., and Freeman, W.: Shock Therapy (Insulin and Metrazol) in the Neuroses, M. Ann. District of Columbia **8**:65, 1939.

7. Freeman, W., and Watts, J. W.: Radical Treatment of Psychoses and Neuroses, Dis. Nerv. System **3**:6, 1942.

immediately after the operation, although he remembers them well; however, he offers pronounced character changes since the operation.

In spite of the superiority of the results of the operative procedure in treatment of obsessive-compulsive neurosis, the small risk of electric convulsive therapy and the occasional good results make advisable a trial of the latter treatment prior to the operation.

One of the purposes of this study was a comparison of the type of response to electric convulsive therapy in neurotic and in psychotic patients. There is one striking difference: Psychotic syndromes which respond favorably to convulsive treatment are broken up suddenly after the third or fourth convulsion, i. e., at a time when the sensorial blurring is still negligible. This characteristic response in psychotic patients was not seen in any of the neurotic patients in our series except those with depressions. Most neurotic patients who improved did so gradually, and only with the appearance of such organic mental symptoms as greater emotional responsiveness, accessibility and suggestibility. The disappearance of neurotic symptoms is rarely as complete as that of certain psychotic syndromes. In some cases, however, the patient forgets his symptoms for a time, shows less emotional response to them and thus may be helped to overcome his illness in a way similar to that observed with the use of sodium amytal. Another element not seen in psychotic persons is the factor of suggestion, as exemplified by patients who were anxious to have the treatment and who improved after one application.

With most of our patients psychotherapy prior to electric convulsive therapy had failed but was used during, as well as after, the shock treatment. In favorable cases the two methods of treatment should be given equal credit because of the better psychotherapeutic accessibility after electric convulsive therapy.[8] This experience is in contrast to that with psychotic patients, with whom excellent results can be obtained without psychotherapy.

The poor response of neurotic patients to electric convulsive therapy and the good results with psychotic patients are of great interest. Conversely, psychologic methods of suggestion and persuasion are helpful in treatment of the neuroses but fail largely with the psychoses. If the effect of electric convulsive therapy were explainable on psychologic grounds, neurotic patients should respond better than psychotic patients. The reverse is true, and even a psychoneurotic admixture in cases of the major psychoses largely diminishes the chance for a remission under shock therapy. It may be added that subconvulsion responses in electric shock therapy, representing in some respects the same psychologic situation for the patient as convulsive responses, are ineffective in psychotic patients,[9] but may lead to improvement in neurotic patients. The difference between the effect on neurotic patients and that on psychotic patients will be of interest for future studies on the effective agent in shock therapy.

CONCLUSIONS

The question of the advisability of electric convulsive therapy of a psychoneurosis is far more difficult than the advisability of such treatment for the major psychoses. For the affective disorders and for schizophrenia the shock therapies are the only methods in general use, and the results are gratifying in a considerable number of patients. For treatment of the neuroses psychologic methods are available, and electric convulsive therapy would be indicated only if the results were superior. Statistical reports on the results of psychotherapy with the neuroses, regardless of the form used, seem to vary within narrow limits, as has been observed only recently with war neuroses.[10] In most statistics on peacetime neuroses the percentage of patients showing improvement ranges between 60 and 70 per cent when persons showing great improvement and those showing slight improvement are considered together.[11] Our figures for electric convulsion therapy reach these values only for a few types of neurotic patients.

On the other hand, the results do not preclude the use of electric convulsive therapy in well selected cases. The actual dangers of this method are so few that one is justified in discussing indications purely from the point of view of expected results. The following recommendations are made on the basis of clinical experience with the series of 65 neurotic patients presented in this paper.

Patients with anxiety neurosis should be excluded from treatment because they have the poorest chance of improvement. The same holds good for patients with conversion hysteria, for

8. Selinsky, H.: The Selective Use of Electro-Shock Therapy as an Adjuvant to Psychotherapy, Bull. New York Acad. Med. **19**:245, 1943.

9. Kalinowsky, L. B.; Barrera, S. E., and Horwitz, W. A.: The "Petit Mal" Response in Electric Shock Therapy, Am. J. Psychiat. **98**:5, 1942.

10. Slater, E.: The Neurotic Constitution, J. Neurol. & Psychiat. **6**:1, 1943.

11. Curran, D.: The Problem of Assessing Psychiatric Treatment, Lancet **2**:1005, 1937.

whom treatment is hazardous because they may react to unpleasant sensations during the treatment with the development of new symptoms. Only when such symptoms may substitute for a depressive episode or when psychotherapy has failed might electric convulsive therapy be tried. Extreme caution should be applied in the selection of patients, and the availability of a simple mechanical method should not prevent the psychiatrist from using a psychologic approach to the patient's psychologic problems.

The situation is different in the case of patients with a severe obsessive-compulsive neurosis of long standing. If such patients have lost their social usefulness and their joy of living and if adequate psychotherapy has failed, or cannot be afforded, an attempt with electric convulsive therapy is justified. A point in favor of the use of electric convulsion therapy is the possibility that neurotic symptoms are the first clinical expression of a psychosis. Occasional improvement in cases of obsessive-compulsive neuroses stimulates speculation regarding the relation of this condition to schizophrenia.

Psychoneurotic depressions should be treated in any case in order to clear the depression, even if the patient may remain neurotic. Many cases of an apparently reactive depression are actually cases of a manic-depressive psychosis, for which convulsive therapy is the treatment of choice. It is equally justifiable to treat the ill defined neuroses of episodic character in which physical complaints and general listlessness are clinical expressions of an underlying depression.

The optimal number of treatments, satisfactorily determined in our experience for the various major psychoses, cannot easily be stated for the neuroses. In patients for whom treatment is intended mainly to relieve tension and to overcome resistance to psychotherapy, a series of a few treatments, with longer intervals and avoidance of confusional states, is preferable. For depressive syndromes the optimum will be six to eight treatments, as given for other depressions. For obsessive-compulsive neuroses twenty treatments, considered as a minimum in treatment of schizophrenia,[12] are given in order to achieve at least temporary disappearance of obsessive thoughts and compulsions.

Our experience does not permit as clear a statement for or against electric convulsion therapy for the psychoneuroses as can be made regarding its value for the manic-depressive and involutional psychoses, as well as for acute schizophrenia. In general, the final results with neurotic patients are unsatisfactory. It may be stated, however, that careful selection of patients and well planned application in combination with psychotherapy lead to fair results in a limited number of patients. The improvement does not resemble, either in type or in degree, that obtainable with a proper application of electric convulsive therapy with certain types of psychoses.

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12. Kalinowsky, L. B.: Electric Convulsive Therapy, with Emphasis on Importance of Adequate Treatment, Arch. Neurol. & Psychiat. **50**:652 (Dec.) 1943.

ABSTRACT OF DISCUSSION

DR. A. E. BENNETT, Omaha: The authors obtained their best results with psychoneurotic depressions. Patients responded after four treatments, but the authors recommend adjunctive psychotherapy. They noted improvement after the fourth treatment in depressions similar to the affective disorders of the psychoses. The only other effect of treatment was organic forgetfulness, similar to narcosis induced by barbiturates. They express the belief that neurotic persons respond poorly to convulsive shock therapy but that psychologic treatment is helpful; yet psychologic treatment fails in therapy of the psychoses. They miss the point, since good results depend on the degree of affective involvement associated with the psychoneurosis or the psychosis. After a certain degree of affective deterioration occurs, psychotherapy is not effective, and a schizophrenic process may be established. Shock therapy is likewise ineffective unless a distinct organic syndrome is superimposed. The authors conclude that the poor results do not exclude the use of electric shock therapy in well selected cases, but they discourage its employment for the treatment of anxiety neurosis and hysteria. They state that "only when such symptoms may substitute for a depressive episode or when psychotherapy has failed should electric convulsive therapy be tried."

The crux of this discussion is whether one can separate the psychoses from the neuroses; many neurotic symptoms are the first expression of a psychosis. Obsessive states often develop into schizophrenia and anxiety states into depressions. Psychoneurotic depressions respond in the same way as reactive, manic-depressive and involutional depressive states; it is a question of the degree of involvement by the affective depression.

In their conclusions the authors are unable to give a clearcut statement for or against convulsive therapy for the psychoneuroses, as they were able to do for manic-depressive and involutional states. I disagree with their contention that the method is effective with acute schizophrenia, but in selected cases good results are obtained.

The authors miss the point which I emphasized in my original paper[13] concerning the value of convulsive shock therapy, namely, that convulsive therapy is a near specific for affective disorders and of little value in schizophrenia. The improvement is determined by the degree of affective reaction of the patient, whether the reaction is schizophrenic or psychoneurotic; this suggests that only two types need be considered from the standpoint of the response to convulsive shock

13. Bennett, A. E.: Convulsive (Pentamethylentetrazol) Shock Therapy in Depressive Psychoses, Am. J. M. Sc. **196**:420 (Dec.) 1938.

therapy: (1) schizophrenic-like states, including obsessive-compulsive, paranoid and certain hysteriod states, which carry a poor prognosis, and (2) affective disorders, including all types of pure depression, manic excitement, involutional depression, psychoneurotic depression, depression with obsessive features and certain catatonic states with depressive features, all of which respond to convulsive shock therapy induced either by drugs or by the electric current.

DR. LLOYD H. ZIEGLER, Wauwatosa, Wis.: The meaning of the diagnosis psychoneurosis varies somewhat from one clinic to another. Sometimes it is applied to the early phases of a disorder which changes so that later a different diagnosis must be made. So-called psychoneurotic manifestations are not infrequent in the course of a substantial psychosis. Neurotic patients may become psychotic. A mild depression is often diagnosed as a neurasthenic (or anhedonic) state. The neuroses encountered in state hospitals are somewhat more tenacious than those met with in office practice. It is apparent that when human nature goes askew, it may not do so in the form of a simple, clearcut, unmixed syndrome. For several years I have been aware of the instability, and often the lack of meaning, of the terminology of diagnostic psychiatry.

If the emotions are meager, undeveloped, poorly used or unwisely conditioned over a long period, electric shock therapy will not give the patient new ones. Hallucinations have been known to disappear after electric shock therapy, but this does not occur regularly. False thinking may right itself after electric shock. An extensive therapeutic survey is needed to demonstrate what effect electric shock therapy (or any other method of treatment, for that matter) may have on numerous disabling symptoms and signs in various combinations and of various durations, regardless of the one or two word psychiatric diagnosis proposed. In this the authors have already made a start.

Compulsive-obsessive neuroses appear to be of two types: One has an insidious onset early in life and is usually tenacious. In my experience, electric shock therapy has not been helpful with this form. Prefrontal lobotomy has benefited some patients. The other type of the neurosis occurs in the form of attacks with fairly abrupt onset and is often associated with considerable depression. This neurosis responds well to electric shock treatment.

Anxiety is a symptom which permeates to the very core of a person, usually disabling him severely. It is a primitive, stubborn and tenacious form of defensiveness. The anxious patient's behavior may be dramatic, and he appeals to the deepest sympathies and concern of persons about him. When anxiety is associated with depression, I have seen it respond to electric shock treatments. Anxiety alone, or conversion symptoms alone, which may be the chief overt defenses of an unstable person, are not responsive to electric shock therapy. There are other methods of dealing with such symptoms somewhat more effectively.

On the whole, electric shock is purely specific in breaking up depressed or elated states, or their clinical equivalents, which come on largely in circumscribed attacks. In so far as these states are complicated by symptoms which are usually called neurotic, the results of electric shock may be attenuated considerably.

Stress in wartime may be so great that any one will break under it sooner or later. Some of these "breaks" appear as syndromes resembling the so-called neuroses. The release of the stress of war, unless it has persisted too long, or unless the person is especially predisposed by nature, often suffices for recovery. This merely shows that predisposition to disorders of human nature exist in every one, but to a variable degree. Some persons are almost immune, and these are sought as the most desirable for active military duty. Rarely does civilian life approximate the quality and degree of the acute and accumulative strain imposed by war. This suggests that the subtly concealed chronic stresses and strains of the neurotic person in civilian life should be investigated and relieved, if possible. I fear that this may ultimately require more than what is called psychotherapy. From what is known of electric shock, it does not benefit more than a few types of patients, as previously mentioned. In this the neurotic and the schizophrenic patients appear to have much in common.

DR. V. E. GONDA, Chicago: There is serious disagreement as to what constitutes one or another type of psychosis or psychoneurosis. Dr. Bennett and Dr. Ziegler have presented diverse opinions. The time seems to have come for a specific agreement in the matter of diagnosis. From the statements of the various speakers, one must conclude that there is practically no known psychosis or psychoneurosis, or any of the subgroups, that could or could not be cured by electric shock therapy. One is indeed lost in the maze of these contradictions.

It is generally accepted that the milder types of psychoneuroses do not respond as well to electric convulsive therapy as do the more serious forms and that the psychoses react with good results only when the treatments are adequate in number and are sufficiently supported by psychotherapy. Whenever, in association with a long-standing psychoneurosis, there develops a depressive state, whether or not it is severe, the patient should be given the benefit of convulsive therapy, if for no other reason than that excellent results are obtained with this method in the treatment of the depressive state.

If it were proved that electric convulsive treatment influences the course of the psychosis more favorably than the course of the psychoneurosis, it might be used in doubtful cases as a differential diagnostic procedure.

DR. TOM B. THROCKMORTON, Des Moines, Iowa: This discussion brings out the conclusion to which I have come, namely, that in patients with true schizophrenia and in persons with various well grounded and fixed fears there is little to be hoped for in improvement or cure from the use of induced convulsive seizures.

I only wish there were some means by which these unfortunate persons could be offered something which would enable them to be rid of their delusions or of their fears, but I am afraid induced convulsive seizures have little promise.

DR. WALTER B. FREEMAN, Washington, D. C.: My first conclusions with respect to the treatment of the psychoneuroses with convulsive shock therapy have been borne out only partially. In other words, the obsessive-compulsive reactions have tended to undergo relapse. On the other hand, my experience in cases of conversion hysteria has been good, even when there was a distinct compensation element.

In treatment of the anxiety states I look on electric shock as a means of overcoming the resistance of the patient to a program of activity designed to allay his symptoms of anxiety. In a number of cases of profound anxiety reactions my associates and I have found that after the electric shock treatment, which was given intensively (perhaps six convulsive attacks in eight days), the patients would walk 5 or 10 miles (0.8 or 1.6 kilometers) a day, and that by observation of such a

regimen during the time of recovery the anxiety could often be overcome to a greater or less extent in the period to follow.

It is fortunate that there is so much disagreement with regard to electric shock therapy of the neuroses, since only by discussion and further experiments can this method of treatment be properly evaluated. For that reason Dr. Kalinowsky's paper is provocative.

DR. LOTHAR B. KALINOWSKY, New York: The difference in the interpretation of Dr. Bennett's results and our own is explained by a difference in concept regarding the line of demarcation between the neuroses and the psychoses. Anxiety is a term which my colleagues and I would not apply to the emotional state of a patient with an agitated depression. Of course, the excellent response of such patients to convulsion therapy is recognized, since Dr. Bennett demonstrated it in the work to which he referred. The complete difference in the response of patients with agitated depression and that of patients with anxiety neurosis is another argument in support of the opinion that the neuroses and the psychoses have a different basis. I do not think a typical anxiety neurosis ever passes over into the psychotic picture of an agitated depression.

I cannot agree with what has been said about electric convulsive therapy in cases of schizophrenia in which good results can be achieved with adequate treatment; that is, when twenty and more treatments are given, even though the patient becomes temporarily free from symptoms after as few as four or five. It is interesting to speculate whether the obsessive-compulsive neuroses which show a good response to electric convulsive therapy are more closely related to schizophrenia. The relation between obsessive-compulsive neurosis and schizophrenia has been frequently discussed. One might look here for the answer to the problem of why a small percentage of patients with obsessive-compulsive neurosis, contrary to the reactions of most other neurotic patients, respond to a method originally advised for the treatment of schizophrenia.

We get the best results from shock therapy in patients with dramatic symptoms. Patients with neurotic symptoms superimposed on a phychosis and patients with borderline conditions in which the personality is well preserved show the poorest response to treatment. I have no explanation to offer for this, but I think it is one of many experiences in shock therapy which are of the greatest interest to the basic concepts of psychiatry and which should be studied without bias from previous psychiatric concepts.

REACTION OF THE MENINGES TO BLOOD

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In the relatively short space of forty years, subarachnoid hemorrhage has passed out of the category of a purely pathologic diagnosis to become a clinical entity capable of being recognized with almost absolute certainty during life. Gull,[1] in speaking of this condition in 1859, stated that "we have at best no symptoms upon which to ground more than a probable diagnosis." However, the introduction by Quincke,[2] in 1891, of lumbar puncture and the establishment by Froin,[3] in 1904, of the criteria necessary to distinguish the cerebrospinal fluid in cases of spontaneous subarachnoid bleeding from that in cases of traumatic lumbar puncture made possible the antemortem diagnosis in a large percentage of cases. Interest in subarachnoid hemorrhage lagged another twenty years, however, until the first careful clinicopathologic study was presented by Symonds,[4] in 1924.

The awakened interest in subarachnoid hemorrhage inevitably has brought forth many problems concerning the cause and therapy of this condition. The increase in trauma of all types, including traumatic subarachnoid hemorrhage, as a result of the present war serves as a further stimulus to investigation of the numerous phases of the subject of intracranial bleeding in general.

Outstanding among the unsolved problems relating to subarachnoid hemorrhage is the question of the harmful or beneficial effects of spinal drainage in the management of patients suffering from this condition. Opinions in the literature are about equally divided on this point. Broadly speaking, observers who advocate the procedure as a therapeutic aid feel that the removal of bloody spinal fluid at frequent intervals combats the danger of increased intracranial pressure and decreases a potential source of irritation to the meninges. Observers who believe that lumbar puncture is unwise, except possibly as a means of confirming the diagnosis, argue that nature will absorb the blood without interference and that the reduction of cerebrospinal fluid pressure can be dangerous only by removal of a protective barrier which, by a tamponade effect, is preventing further bleeding from the already ruptured vessel.

A factor which must be considered in evaluating the problem of therapeutic lumbar puncture in cases of subarachnoid hemorrhage is the reaction of the meninges to blood, for if it were found that blood is well tolerated by the pia-arachnoid one of the major arguments in favor of spinal drainage would be nullified. Accordingly, it was the purpose of this study to determine whether or not autogenous blood, in the absence of infection, is capable of causing a reaction in the meninges and, if so, to find out the nature of that reaction.

The earliest published suggestion of a meningeal reaction following spontaneous subarachnoid hemorrhage is to be found in a case report by Bramwell,[5] in 1886, in which he described "a localized collection of corpuscles, apparently indicative of a localized periarteritis" around the ruptured aneurysm of a patient who had died of spontaneous subarachnoid hemorrhage. From the experimental standpoint, Essick,[6] in 1920, investigated the effect of laked blood on the meninges of cats. He observed that full-blown sterile meningitis developed within six hours and was gradually replaced in forty-eight hours by large mononuclear phagocytes, which he observed forming from the arachnoid lining cells.

Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurology and Psychiatry.

1. Gull, W.: Cases of Aneurism of the Cerebral Vessels, Guy's Hosp. Rep. **5**:281-304, 1859.

2. Quincke, cited by Levinson, A.: Cerebrospinal Fluid in Health and in Disease, St. Louis, C. V. Mosby Company, 1919, chap. 1, pp. 17-30.

3. Froin, G.: Les hémorragies sous-arachnoïdiennes et le mécanisme de l'hématolyse en général, Paris, G. Steinheil, 1904.

4. Symonds, C. P.: Spontaneous Subarachnoid Haemorrhage, Quart. J. Med. **18**:93-122 (Oct.) 1924.

5. Bramwell, B.: Clinical and Pathological Memoranda, Edinburgh M. J. **32**:1-11 (July) 1886.

6. Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulus of Particulate Matter, Contribution 272, Carnegie Institution of Washington, 1920, pp. 377-388.

Weed [7] had previously pointed out that the morphologic character of these mesothelial lining cells varied with their function. Essick confirmed this observation when he noted that in response to laked blood the normally flat lining cells passed through stages of becoming rounded, of enlarging, of assuming active phagocytosis while still attached to the trabeculae and, finally, of breaking off as free phagocytes in the cerebrospinal fluid. Essick's work on cats has recently been confirmed by Finlayson and Penfield,[8] who used human subdural hematoma fluid as the irritant. In the same year Ayer [9] arrived at essentially the same conclusions, using other experimental animals. Still further confirmation was offered by Woollard,[10] in 1924.

That blood can cause not only a transient meningitic response but permanent fibrosis and obstruction to the flow of cerebrospinal fluid was shown in pups and adult dogs by Bagley,[11] in 1927. He observed that the intrathecal injection of blood caused symptoms varying in degree of intensity up to severe convulsions. Studies showed an increase of fibrous tissue in the meninges after several weeks and, in many of the pups, moderate ventricular dilatation.

In an excellent series of papers, Bagley [12] bridged the gap between experimental and clinical observations by means of a study of the meninges in cases representing various types of cerebral and subarachnoid hemorrhage. He observed a transient meningeal reaction with marked phagocytosis and, at a later stage, fibrotic thickening of the meninges, which was most pronounced at the base of the brain and in the sulci of the cerebral hemispheres, where the pia was matted together by fibrous tissue. In 1 of his cases, that of an infant 18 days of age, he attributed the presence of internal hydrocephalus to fibrosis and obstruction in the region of the foramens of Magendie and Luschka. In another case of fibrosis of the leptomeninges following subarachnoid hemorrhage a communicating type of hydrocephalus suggested interference with absorption of the cerebrospinal fluid along the longitudinal sinus. Bagley concluded that patients with subarachnoid hemorrhage should be treated by drainage of the irritant fluid. Mild hemorrhage in adults may be followed by complete recovery without drainage, but hemorrhage in infants, if untreated, frequently leads to hydrocephalus, muscular rigidity and epilepsy.

In many of Bagley's cases the condition either developed after operation or was the result of trauma to the head. The same is true of the human material studied by Finlayson and Penfield, since their interest lay primarily in a clinicopathologic investigation of the effect of blood in the subarachnoid space following intracranial surgical procedures. Accordingly, in the only two large series of cases reported in which the meningeal reaction to blood was studied in man, the factors of (1) possible infection, either postoperative or secondary to fracture of the skull, and (2) exposure of the meninges to the atmosphere introduced variables which might theoretically influence the meningeal response.

A review of the many reports of cases in the literature dealing with spontaneous subarachnoid hemorrhage proved disappointing with regard to mention of meningeal changes. Necropsy reports are confined primarily to a description of the source of the hemorrhage or of the type of aneurysm, if one was present. Reports by Herndon,[13] Strauss, Globus and Ginsburg [14] and Turner [15] contain the mention of a meningeal reaction, with the presence of polymorphonuclear leukocytes, lymphocytes and, later, fibrosis. In none of these cases were there symptoms or evidence at necropsy of interference with the flow or absorption of cerebrospinal fluid. Smith[16] and Merwarth and Freiman,[17] however, each reported a case of hydrocephalus following subarachnoid hemorrhage in a child. In each case

7. Weed, L. H.: An Anatomical Consideration of the Cerebro-Spinal Fluid, Anat. Rec. **12**:461-496 (May) 1917.

8. Finlayson, A. I., and Penfield, W.: Acute Postoperative Aseptic Leptomeningitis: Review of Cases and Discussion of Pathogenesis, Arch. Neurol. & Psychiat. **46**:250-276 (Aug.) 1941.

9. Ayer, J. B.: A Pathological Study of Experimental Meningitis from Subarachnoid Inoculation, Monograph 12, Rockefeller Institute for Medical Research, 1920, pp. 26-44.

10. Woollard, H. H.: Vital Staining of the Leptomeninges, J. Anat. **58**:89-100 (Jan.) 1924.

11. Bagley, C., Jr.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System, Tr. South S. A. **40**:369-392 (Dec.) 1927; Arch. Surg. **17**:18-81 (July) 1928.

12. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of Four Types, with Surgical Considerations, Tr. South S. A. **44**:448-484 (Dec.) 1931; Arch. Neurol. & Psychiat. **27**:1133-1174 (May) 1932; footnote 11.

13. Herndon, R. F.: Spontaneous Subarachnoid Hemorrhage, Illinois M. J. **75**:73-80 (Jan.) 1939.

14. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage: Its Relation to Aneurysms of Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **27**:1080-1132 (May) 1932.

15. Turner, C. C.: Spontaneous Subarachnoid Hemorrhage, South. M. J. **34**:949-954 (Sept.) 1941.

16. Smith, W. A.: Spontaneous Subarachnoid Hemorrhage, South. M. J. **23**:494-500 (June) 1930.

17. Merwarth, H. R., and Freiman, I. S.: Hydrocephalus Following Subarachnoid Hemorrhage: Report of Case with Pathologic Study, Brooklyn Hosp. J. **1**: 149-157 (July) 1939.

fibrosis and obliteration of the subarachnoid space were noted post mortem; in Merwarth and Freiman's case the hydrocephalus was of the communicating type.

MATERIAL AND METHODS

The material used in this study was selected from a series of 114 cases in which necropsy was performed at the Mayo Clinic from 1922 to 1943 inclusive, in each of which an intracranial aneurysm was noted. To eliminate as far as possible the existence of an unrecognized infection which could account for any meningeal changes, three types of cases were excluded, for the reasons indicated: (1) cases in which the subarachnoid hemorrhage followed trauma to the head, because of the possibility of fracture of the skull and bacterial contamination of the subarachnoid space; (2) cases in which craniotomy, laminectomy or other surgical procedure involving the central nervous system had been performed, as well as a few cases in which a ventriculogram or an air encephalogram had been made, because of the possible effect of oxygen on the meninges, and (3) cases in which a systemic disease, such as active tuberculosis had been present. One case in which the serologic reactions were positive for syphilis was included, but studies of the spinal fluid before and after the subarachnoid hemorrhage showed no evidence of syphilis of the central nervous system. In every case selected an aneurysm was observed rupture of which could reasonably be assumed to be the source of the bleeding. The presence of such a lesion was established as a criterion in order that an unknown, and possibly infected, source of the hemorrhage should not be overlooked. No attempt was made to separate congenital and arteriosclerotic aneurysms. Cases of rupture of mycotic or traumatic aneurysm were not included. Of the 114 cases, 53 met all the aforestated requirements.

As controls, 26 cases were selected in which death resulted from disease unrelated to the central nervous system, in which there had been no symptoms suggesting disease of the central nervous system and in which no changes in the brain or the spinal cord were noted at necropsy. These cases were chosen in such a way that the age and sex distributions were proportionately the same as those in the 53 cases of subarachnoid hemorrhage.

From four to nine microscopic sections were studied in every case. As a rule, sections were taken from the area of maximal hemorrhage near the ruptured aneurysm, at the base of the brain, over the convexity of the cerebral hemispheres and from the spinal cord. The tissues were stained with hematoxylin and eosin, Mallory's phosphotungstic acid hematoxylin, the Mallory-Heidenhain and Van Gieson stains and the berlin blue stain for iron.

The duration of the hemorrhage prior to death was necessarily based on clinical judgment, but in nearly every case the onset was sufficiently dramatic to leave little question as to when the first rupture took place. The patients had survived various lengths of time, from a few minutes to six months. One patient had died ten years after the rupture, of an unrelated disease, and another had died of a recurrent subarachnoid hemorrhage twelve years after the original hemorrhage.

The youngest patient was 18 and the oldest 84 years of age at death. The average age was 49.4 years. In the majority of cases (33) the hemorrhage had occurred between the ages of 40 and 60. The average age in this group was about 10 years higher than that in most of the reported series of cases of spontaneous subarachnoid hemorrhage.[18] On the other hand, the average age in the fatal cases in the series reported by Richardson and Hyland[19] was 50, and the evidence in the present series tends to confirm the impression of these authors that the prognosis becomes worse with advancing years.

None of the reports in the literature shows any consistent preponderance of patients of either sex. Of the present series of 53 patients, 30 were males and 23 females. The slightly greater incidence (56.6 per cent) of the condition in men is not considered significant.

ASSOCIATED PATHOLOGIC CONDITIONS

In 7 cases necropsy was limited to the head. In the 46 cases in which complete necropsy was performed two associated pathologic conditions stood out. The heart was hypertrophied in 24 instances, this observation offering confirmation of the clinically noted frequent occurrence of hypertension among patients with spontaneous subarachnoid hemorrhage. In 23 cases one or more congenital defects were present. These included ectopic adrenal, pancreatic or splenic tissue, duplication of the ureter, Meckel's diverticulum and malrotation of the colon. This relation has been noted by many investigators and substantiates the hypothesis first presented by Eppinger[20] that intracranial aneurysms develop from congenital defects.

Associated Intracerebral and Intraventricular Hemorrhage.—In 25 cases the subarachnoid hemorrhage was unaccompanied by bleeding into the substance of the brain or into the ventricles. In 26 other cases there was associated intracerebral hemorrhage, and in 20 of these cases the blood had broken through the ependyma and formed clots in the ventricles. In 2 cases of subarachnoid without intracerebral hemorrhage the intraventricular fluid was slightly blood stained, but in every instance in which there was clotted blood in the ventricles an associated intracerebral hemorrhage was present.

18. Neal, J. B.: Spontaneous Meningeal Hemorrhage, J. A. M. A. **86**:6-8 (Jan. 2) 1926. Russel, C. K.: Spontaneous Subarachnoid Haemorrhage, Canad. M. A. J. **28**:133-140 (Feb.) 1933. Tucker, J.: Spontaneous Subarachnoid Hemorrhage: A Brief Review of Fifty Consecutive Cases, Cleveland Clin. Quart. **7**:152-157 (April) 1940. Symonds.[4]

19. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms: A Clinical and Pathological Study of Subarachnoid and Intracerebral Haemorrhage Caused by Berry Aneurysms, Medicine **20**:1-83 (Feb.) 1941.

20. Eppinger, cited by Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:239-284 (Nov.) 1930.

The incidence of intracerebral hemorrhage in nearly half the cases is surprisingly high and merits further discussion. As was to be expected, the majority of the intracerebral hemorrhages occurred in the frontal or the temporal lobe, usually at the base. None was observed in the occipital lobe, the cerebellum or the brain stem.

MENINGEAL RESPONSE TO SUBARACHNOID BLEEDING

Gross examination of the meninges in cases in which the patients had died at various intervals after rupture of an intracranial aneurysm failed to reveal any consistent change other than variable amounts of blood in different stages of degeneration. In all cases in which the patient had survived the first few days of the illness, only to die later of subarachnoid hemorrhage, there was clinical or postmortem evidence, or evidence in the cerebrospinal fluid, of fresh bleeding on one or more occasions. In some instances such an episode had occurred as many as four times within a month before the patient died. These attacks of bleeding cannot be considered evidence of recurrent subarachnoid hemorrhage in the usual meaning of the term, since they invariably represented fresh bleeding from the same site before the ruptured artery had had a chance to heal. This point is stressed because it constitutes an unavoidable limitation to determination of the duration of any phase of the meningeal reaction following exposure to blood. The ideal situation, of course, would be a series of cases in each of which there had been a single massive hemorrhage, with no further bleeding until death. If, however, the meninges are exposed to a new hemorrhage at several, irregular intervals prior to death, each hemorrhage will exert an effect on the reaction and will modify the postmortem appearance accordingly. This limitation was constantly kept in mind in the attempt to evaluate the changes now to be described.

Sudden Death.—In 9 of the 53 cases death had taken place within ten minutes of onset of the first symptom, and the majority of the patients were totally unaware of impending catastrophe at the time they became ill. Spontaneous subarachnoid hemorrhage is probably the commonest intracranial cause of nontraumatic sudden death of apparently healthy persons. Martland [21] obtained evidence of this condition in 2 per cent of 2,500 necropsies performed on the bodies of persons who had died suddenly without a history or external evidence of violence. The opinion expressed by Ayer [22] that death may follow spontaneous subarachnoid hemorrhage in as short a time as thirty-five minutes, but is never instantaneous, is at variance with the frequency of sudden death in the present series.

Microscopically, the subarachnoid space was observed to be filled with fresh blood cells, which passed into the sulci but were sharply delimited by the pia and arachnoid. Blood cells were rarely seen in the Virchow-Robin perivascular spaces; it was not common to see blood filling a sulcus but failing to enter the mouth of a Virchow-Robin space which connected with that sulcus. The reason for failure of the blood to penetrate these perivascular spaces is probably to be found in their small diameter and in the fact that the normal direction of flow along them is centrifugal, toward the subarachnoid space, as was shown by Weed [23] and Hassin.[24] As was to be expected, the blood was most prominent around the base of the brain, in the large cisterns, since the site of hemorrhage was in this region. However, considerable blood also was diffused over the convexity of the cerebral hemispheres and down the spinal cord to the theca. No reaction was seen in the meninges.

Death in One to Four Hours.—The earliest evidence of meningeal reaction was seen in cases in which the patients had survived two hours. The evidence consisted of small collections of polymorphonuclear leukocytes around the blood vessels of the pia. The microscopic appearance of the meninges was otherwise identical with that seen in examination of the tissues in the cases in which sudden death had occurred.

Death in Four to Sixteen Hours.—Patients who had survived four hours had sustained a more intense polymorphonuclear reaction, which had tended to become diffuse throughout the pia-arachnoid (fig. 1). No difference was noted between the reaction at the bottoms of the sulci and that over the surface of the brain. Neither was any constant relation noted between the severity of the reaction, on the one hand, and the anatomic portion of the brain, the amount of free blood or the proximity to the source

21. Martland, H. S.: Spontaneous Subarachnoid Hemorrhage and Congenital "Berry" Aneurysms of the Circle of Willis, Am. J. Surg. **43**:10-19 (Jan.) 1939.

22. Ayer, W. D.: So-Called Spontaneous Subarachnoid Hemorrhage: A Résumé with Its Medicolegal Consideration, Am. J. Surg. **26**:143-151 (Oct.) 1934.

23. Weed, L. H.: Studies on Cerebro-Spinal Fluid: III. The Pathways of Escape from the Subarachnoid Spaces with Particular Reference to the Arachnoid Villi, J. M. Research **31**:51-91 (Sept.) 1914.

24. Hassin, G. B.: Notes on the Nature and Origin of the Cerebrospinal Fluid, J. Nerv. & Ment. Dis. **59**:113-121 (Feb.) 1924.

of the hemorrhage, on the other. After about four hours an outpouring of lymphocytes was noted, and these cells, like the polymorphonuclear leukocytes, were first seen around the pial vessels, this occurrence suggesting that both types of cells enter the meninges from the blood vessels (fig. 2).

Death in Sixteen to Thirty-Two Hours.—Both types of leukocytes increased in number and were more diffusely distributed through the pia-arachnoid at this stage than in the four to sixteen hour stage. The reaction was still predominantly polymorphonuclear. At no time, however, was the response of the polymorphonuclear cells comparable in intensity to that seen in a case of acute purulent bacterial meningitis.

It was during this interval, approximately twenty-four hours after the hemorrhage, that

Fig. 1.—Polymorphonuclear leukocyte response to subarachnoid bleeding in the meninges of a patient who had survived five days. Large numbers of polymorphonuclear leukocytes, mixed with degenerating blood, can be seen scattered through the subarachnoid space. × 275.

the mesothelial cells which line the borders of the subarachnoid space and the surface of the arachnoid trabeculae began to take part in the reaction. Normally flat, elongated cells, they now became swollen, rounded and actively phagocytic. This phagocytic tendency was well developed in mesothelial cells which were still attached to the arachnoid or to its trabeculae. Cells often could be traced in all stages of change, from their quiescent state through the phases of their swelling and becoming phagocytic, to their final breaking away from the trabeculae and becoming free cells. Coincident with these changes in the mesothelial cells was the appearance of large numbers of active phagocytes in the subarachnoid space, and the relationship between these free phagocytes and the mesothelial cells cannot be disputed.

During this period was noted the first evidence of breakdown of blood, in the appearance of brown pigment and iron. The pigment and iron occurred both free in the subarachnoid space and within the cytoplasm of polymorphonuclear leukocytes and phagocytes.

Death in Three Days.—During the third day after the accident all cells had increased in frequency of appearance. The polymorphonuclear cell reaction was at its height, but, because of the rapid increase in the number of lymphocytes and phagocytes, the polymorphonuclear leuko-

Fig. 2.—Perivascular collections of lymphocytes around pial blood vessels in the mouth of a sulcus in the parietal cortex of a man aged 51. Two vessels are visible, with many lymphocytes in the adjacent subarachnoid space. × 275.

cytes now formed less than half the cellular element in the fairly intense meningitic reaction. The original perivascular arrangement of the leukocytes in the meninges could no longer be detected except in rare instances. The activity of the mesothelial cells and the occurrence of free mononuclear phagocytes were more evident. The mesothelial cells were extremely active and often contained within their cytoplasm several whole red blood cells, bits of pigment and iron and degenerated leukocytes (fig. 3 *a* and *b*).

An outstanding feature of the reaction at every stage was the considerable variation in the appearance of different portions of the brain, and even in different parts of the same microscopic section. In some locations the cells were exclusively polymorphonuclear leukocytes; in others, entirely lymphocytes, and in still others the various cell types were diffusely mixed.

Death in Seven Days.—By the end of a week the polymorphonuclear cell reaction had subsided. In no case in which the patient lived longer than seven days were polymorphonuclear leukocytes seen unless there had been fresh bleeding during the week before death. The intensity of the cellular reaction was at its peak and was

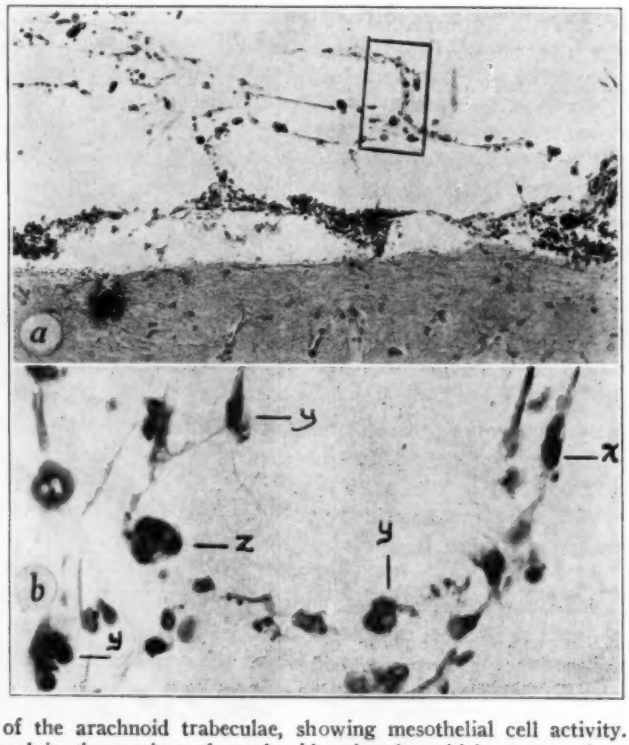

Fig. 3.—Lining cells of the arachnoid trabeculae, showing mesothelial cell activity. (*a*) Pigment, red blood cells and debris are trapped in the meshes of arachnoid trabeculae which traverse the subarachnoid space (× 95). (*b*) Higher magnification (× 575) of the blocked area indicated in *a*. Here, *x* indicates a resting lining cell; *y*, various stages of swelling of the lining cells, some of which are phagocytic while still attached to the trabeculae, and *z*, a lining cell which has broken off as a free phagocyte. Several whole red blood cells can be seen in the cytoplasm.

composed about equally of lymphocytes and phagocytes (fig. 4). Pigment and iron were increased in amount, and intact red blood cells still could be identified.

Death in Ten Days.—At this stage there first appeared definite fibrosis in the leptomeninges. The amount of fibrous tissue in the pia-arachnoid of normal persons varies tremendously with the age of the patient and with the portion of the brain examined. Fibrosis is increasingly evident with advancing years and is more prominent along the parasagittal portions of the cortex and over the pons, medulla and spinal cord than elsewhere. However, in a given portion, this physiologic increase in fibrous tissue is diffusely equal in amount and never, in my experience, passes from pia to arachnoid to obliterate the subarachnoid space. If patients lived more than ten days after subarachnoid hemorrhage, pathologic fibrosis was never excessive, and the fibrous tissue was rarely thicker than the maximum amount present in the meninges of elderly control subjects. The fibrosis following subarachnoid hemorrhage, however, differed in three significant respects from that seen in the controls: First, it was observed characteristically in contact with blood in the subarachnoid space; second, the areas of fibrosis were patchy, being dense in some areas and slight or absent in adjacent parts; and, third, in the end stage, when the blood had disappeared from a given area, the fibrosis was seen to bind pia to arachnoid (fig. 5 *a* and *b*) or pia to pia in a sulcus, and thus to obliterate the subarachnoid space. The fibrosis was noted with about equal frequency in various parts of the brain and appeared as commonly over the surface of the

hemispheres as it did in the depths of the sulci.

The variation in the degree of fibrosis in different cases was striking. In some cases there were definite changes in every section examined; in others fibrosis was present in only one or two areas, and in nearly half the cases in which survival was for ten or more days no definite fibrotic alteration was seen. The failure to discover fibrosis in such a large percentage of cases was probably due to two factors: First, the patchy nature of the fibrosis was such that five or ten sections taken at random might well miss any fibrotic tissue that was present. Second, the response in the individual case was probably variable; while fibrosis developed in ten days in some cases, the process might take several weeks in others. Of the cases in which the patients had lived seven weeks or longer after the first hemorrhage, postmortem examination in only 1 failed to reveal distinct fibrotic changes.

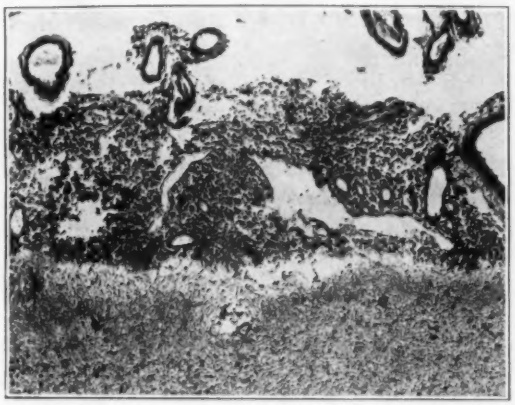

Fig. 4.—"Lymphocytic meningitis" in a case in which the patient survived eight days after spontaneous subarachnoid hemorrhage. Practically all the cells are lymphocytes. The reaction stops abruptly at the surface of the cortex. The blood vessels are open and show no evidence of being actively involved in the inflammatory process. × 50.

No correlation was observed between the age of the patient and the amount or time of appearance of the fibrosis.

Death in Two Weeks or More.—In all the cases of survival for from two weeks to six months there were recurrent episodes of bleeding. Postmortem examination of the meninges disclosed, in addition to the fibrotic changes previously described, variable amounts of blood pigment, iron, leukocytes and phagocytes, in keeping with the presence of more recent hemorrhages. Activity of the mesothelial cells and the presence of free phagocytes and lymphocytes persisted as long as there was any evidence of blood or of products of breakdown of blood in the subarachnoid space. This is in contrast to the polymorphonuclear cell response, which subsided in about a week unless further hemorrhage occurred.

In 1 case the patient had survived ten years and had died of an unrelated illness; the meninges were free of blood or cellular reaction, but definite patchy fibrosis was seen. In another case the patient had died twelve years after the primary subarachnoid hemorrhage and twelve hours after a recurrent hemorrhage. Necropsy revealed changes in the pia-arachnoid consistent with those observed post morten in other persons in the series who had died between four and sixteen hours after the vascular accident.

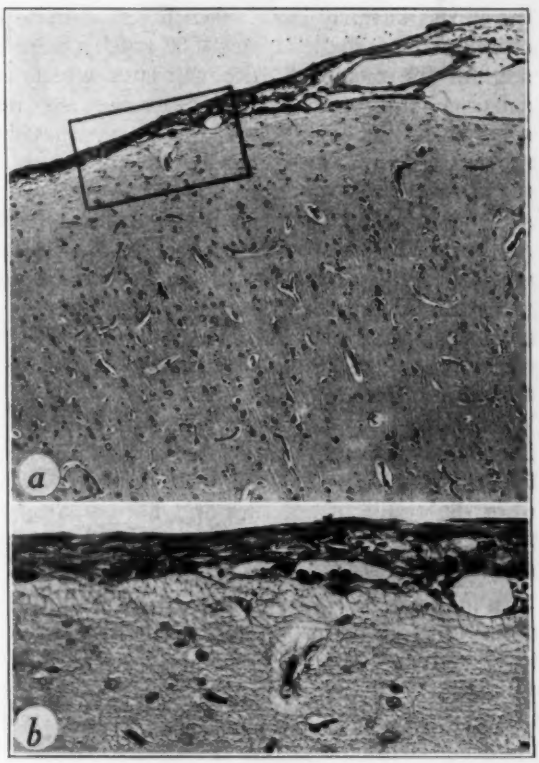

Fig. 5.—Obliteration of the subarachnoid space by fibrosis. Death occurred five and a half months after the initial subarachnoid hemorrhage. (*a*) On the right can be seen the open subarachnoid space, bounded by pia below and by arachnoid above. Toward the left the two membranes approach each other and fuse. × 65. (*b*) The point of fusion, from the blocked area in *a*. The two membranes can no longer be identified in the solid sheet of fibrous tissue. × 200.

In addition, evidence of the woman's primary hemorrhage persisted in the form of fibrosis.

At no time were changes noted in the blood vessels of the pia. The existence of thrombosis or of reactive arteritis with obliteration of the lumen, such as is seen with tuberculous meningitis, was considered theoretically possible, but no evidence for this was forthcoming from

microscopic examination. The most outstanding feature of the reaction at every stage after the immediate diffusion of blood through the subarachnoid space was the irregular, patchy distribution of the cellular and, later, of the fibrotic response.

COMMENT

In view of the signs and symptoms of severe meningeal irritation which usually accompany spontaneous subarachnoid hemorrhage, it would indeed be surprising if there was not microscopic evidence of a reaction in meninges exposed to the blood. Correlation between clinical and pathologic signs during the first few weeks of the illness is fairly close. Much less definite is correlation of the end stage of patchy fibrosis seen in the meninges with the later effects of subarachnoid hemorrhage. Sequelae are not common in this condition; if the patient survives the initial insult, he is faced with the constant threat of recurrence, but as a rule he is not subjected to other severe or permanent ill effects. An exception to this, of course, is the patient whose ruptured aneurysm produces intracerebral, as well as subarachnoid, hemorrhage. Occasionally, also, palsy of one of the cranial nerves is encountered, and this is generally accepted as the result of bleeding into the nerve or its sheath. When such palsy occurs, it is present as a rule from the onset of the illness; it does not develop later in the course, as might be expected if it were the result of scarring and fibrosis around the nerve as this structure passes through the subarachnoid space.

In patients in the younger age group there occurs occasionally an obstructive type of hydrocephalus after subarachnoid hemorrhage, and this may be correlated with obliteration of the cerebrospinal fluid pathways by fibrosis. In this series of cases evidence of hydrocephalus was not present. The patchy nature of the fibrosis makes one hesitate to ascribe to it the ability to interfere significantly with the flow of cerebrospinal fluid, unless fibrosis were to occur in particularly vulnerable spots, such as at the foramens of Magendie and Luschka.

It was noted that among the 8 cases of sudden death in which a past history could be obtained there were no instances of associated intracerebral hemorrhage, although the incidence of intracerebral hemorrhage in the entire series was nearly 50 per cent. This fact, together with the appearance, represented in figure 6, of obliteration of the mouth of a sulcus, suggested the possibilty that fibrosis following an earlier hemorrhage might isolate an aneurysm from the general subarachnoid space and, at a later rupture, cause the blood to break into the brain substance as the line of least resistance. Investigation of this point showed that this was not necessarily true. The incidence of intracerebral hemorrhage in cases of survival for longer than ten days after the initial subarachnoid hemorrhage was essentially the same as that in cases of death in less than ten days. Ten days was taken as the division point because it was at this time that fibrosis was first seen. Furthermore, the incidence of intracerebral hemorrhage was no greater in the cases in which necropsy revealed meningeal fibrosis than it was in the cases in which no fibrosis was seen. Nevertheless, the fact remains that a subarachnoid hemorrhage so severe as to cause sudden death rarely, if ever, produces intracerebral bleeding, whereas such bleeding is a common catastrophe later in the course if the patient survives the first few hours. Bagley, likewise, noted that intracerebral hemorrhage usually occurs during

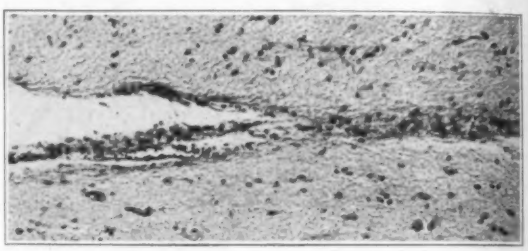

Fig. 6.—Obliteration of the subarachnoid space in a cerebral sulcus. Death occurred three months after the first subarachnoid hemorrhage. The surface of the brain is to the right, beyond the area shown in the photograph. The two adjacent surfaces of pia have been fused as a result of fibrosis. × 90.

the course of a rather mild subarachnoid hemorrhage. It is suggested that the large amount of clotted blood observed at necropsy around the aneurysmal site might serve to isolate the aneurysm from the general subarachnoid space, and that the product of any further bleeding would thus be forced into the brain substance. At a later stage organization of the clot and fibrosis might act in the same manner to prepare the way for a subsequent intracerebral hemorrhage. In other words, if an aneurysm is so situated that blood coming from it can rapidly flow through the subarachnoid space, the brain will not be invaded. If, however, the diffusion of blood is obstructed either by the clot of a previous hemorrhage or by fibrosis, intracerebral bleeding is likely to result.

The source of the various elements seen in the previously described reactions is of interest. The perivascular arrangement of both polymor-

phonuclear leukocytes and lymphocytes during the early stages of their appearance points to a hematogenous origin, the cells possibly entering the meninges and the subarachnoid space by direct passage through the walls of the pial vessels. The coincident appearance of activity of mesothelial lining cells and of free mononuclear phagocytes in the cerebrospinal fluid and the meninges suggests the derivation of the probably manifold. Normally, fibroblasts can be seen in both the pia and the arachnoid, and these presumably contribute to the organization of clotted blood in the subarachnoid space. Moreover, in the early stages of organization occasionally evidence of the laying down of fibroblasts and collagen fibers can be seen, not only at the periphery of the clot but along the surfaces of the many trabeculae enmeshed in

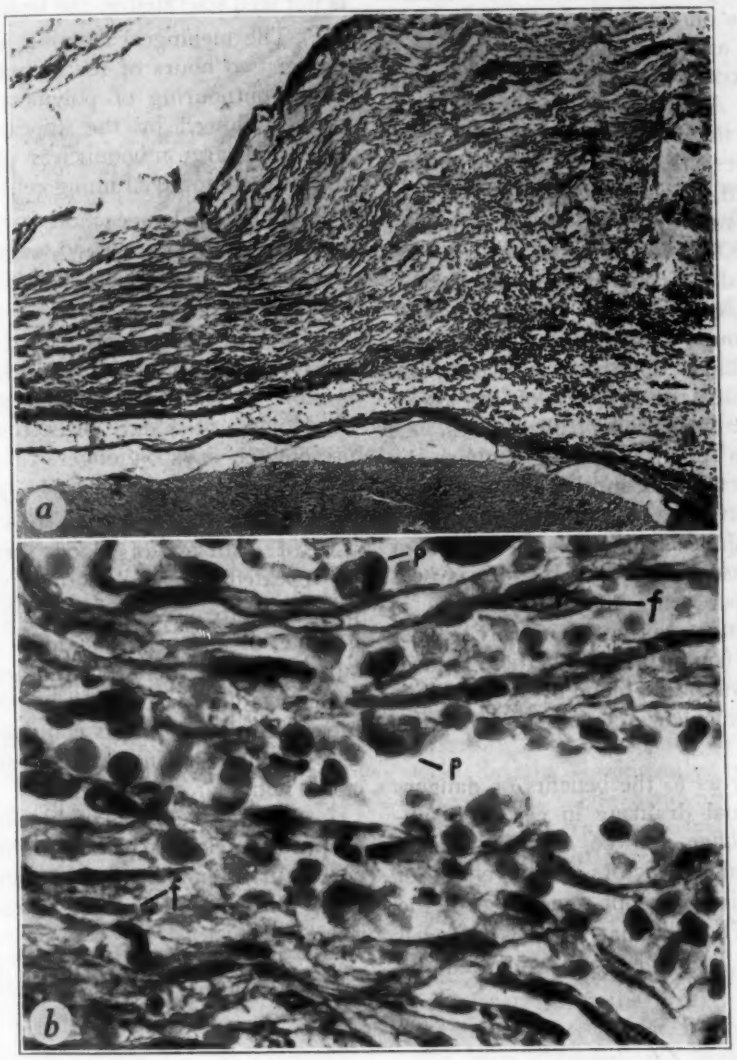

Fig. 7.—Organization of subarachnoid hemorrhage. (*a*) Many delicate strands of fibrous tissue can be seen passing through the blood parallel to each other and to the surface of the arachnoid. Mallory-Heidenhain stain; × 50. (*b*) A higher magnification (× 800) of the arachnoid trabeculae in the midst of an area of subarachnoid blood. Individual fibroblasts (*f*) can be seen in close proximity to the trabeculae. Fully developed phagocytes are indicated by *p*. Hematoxylin-eosin stain.

latter cells from the former. This is confirmed by the observation of phagocytosis in the mesothelial cells before they lose their attachment to the arachnoid trabeculae, as well as by the presence of cells in all stages of transition, from quiescent lining cells to free phagocytes laden with debris. The origin of the fibroblasts is it (fig. 7 *a* and *b*). The potentialities of the mesothelial cells have been emphasized by Weed, and their ability to form phagocytes has been discussed. That they may also contribute to the formation of fibroblasts is suggested by the procedure of organization outward from the individual trabeculae.

An attempt was made to determine the effect, if any, of therapeutic spinal drainage on the meningeal response to blood. Unfortunately, in no case did the patient receive what might be considered intensive spinal drainage. The greatest number of lumbar punctures done in any single case was nine, in a period of sixteen days; the largest volume of spinal fluid removed was 119 cc., in eight punctures over a period of twenty-one days. The series was divided into three groups on the basis of the amount of spinal drainage, and the meningeal reaction in each group was compared with that in the other groups. Group A was composed of cases in which not more than one lumbar puncture had been done and less than 15 cc. of spinal fluid had been removed. Group C consisted of cases in which five or more punctures had been done and a total of 50 cc. or more of spinal fluid had been removed. Group B was intermediate between groups A and C. No significant difference in the groups was noted with respect to the amount of blood, pigment and iron, the leukocytic response, the activity of the mesothelial cells or the formation of phagocytes. Of the cases in group A (drainage not established), in which the patients had survived long enough for fibrosis to develop, the amount of fibrous tissue in the meninges had increased in 55 per cent. Of the cases in group B fibrosis was observed in 36 per cent, and of the cases in group C, this change was noted in only 25 per cent. While far from conclusive, these figures suggest that removal of the blood by spinal drainage decreases the incidence of permanent meningeal scarring.

The controversy as to the benefits or dangers of therapeutic spinal drainage in cases of subarachnoid hemorrhage can be settled only by consideration of many factors. The effect of blood on the meninges is but one phase of the entire problem. The fact that blood is not well tolerated by the meninges, as evidenced by the transient cellular reaction and permanent fibrosis, suggests strongly that if it can be done safely, removal of as much blood as possible by spinal drainage will lessen the severity of the symptoms of meningeal irritation in a case of subarachnoid hemorrhage.

CONCLUSIONS

1. Autogenous blood in the subarachnoid space is not well tolerated by the leptomeninges in man.

2. The meningeal reaction to blood is evident within two hours of the hemorrhage and begins as an outpouring of polymorphonuclear leukocytes, followed by the appearance of lymphocytes and large mononuclear phagocytes derived from the mesothelial lining cells of the arachnoid.

3. This cellular reaction is transient and persists only as long as blood, or products of breakdown of blood, are demonstrable in the subarachnoid space.

4. Permanent effects occur in the form of patchy fibrosis of the pia-arachnoid, with obliteration of the subarachnoid space. This can be demonstrated only after the blood has been present ten days or longer.

5. From this study, no conclusion can be drawn as to the effect on this meningeal reaction of drainage of bloody cerebrospinal fluid by repeated lumbar punctures.

6. Rupture of an intracranial aneurysm is capable of producing sudden death. Patients suffering from this accident rarely, if ever, have an associated intracerebral hemorrhage, although intracerebral bleeding is common among persons who survive the immediate insult, only to succumb hours or days later.

7. An intraventricular hemorrhage sufficient to produce clotted blood in the ventricles will not occur after rupture of an intracranial aneurysm unless an associated intracerebral hemorrhage exists.

The Mayo Clinic.

ELECTROENCEPHALOGRAPHIC EVALUATION OF PSYCHOPATHIC PERSONALITY

CORRELATION WITH AGE, SEX, FAMILY HISTORY AND ANTECEDENT ILLNESS OR INJURY

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In a previous report [1] it was indicated that adults who exhibited certain personality deviations presented abnormalities in the electroencephalogram. Of 44 patients with a condition diagnosed as "psychopathic personality," 23, or 52 per cent, had electroencephalograms which did not meet our criteria of normal. Several other investigations have been made independently, and all have revealed a similar relation. Hill and Watterson [2] reported that 48 per cent of 151 patients with a disorder diagnosed as "psychopathic personality" had abnormal electroencephalograms. Silverman,[3] in a study of the more extreme and dangerous criminal psychopathic personalities, found that 80 per cent of 75 patients exhibited abnormal or borderline abnormal tracings. In view of the essential agreement of these three reports, the problem of the meaning of this relation arises.

One of the inherent difficulties in a study of this kind is the inability to define meaningfully the concept "psychopathic personality." Maughs,[4] in his historical review, pointed out the continuous changes in the concept, and Preu [5] emphasized the negative side in arriving at a diagnosis. Unfortunately, no symptoms are considered specific for or pathognomonic of the psychopathic personality. The term is applied to various inadequacies or deviations of the personality, when they are not due to mental deficiency, structural disease of the brain, epilepsy or definite mental disease (i. e., psychoses and psychoneuroses), which prevent socially acceptable adaptation of the person to his environment. This concept is so broad that the cross sectional picture may include symptoms produced by encephalitides, encephalopathies, epileptic states and postpsychotic defective states, as well as similar symptoms due to psychologic factors. Longitudinal studies and the anamnesis allow many persons to be categorized in relation to the important etiologic factors and thus excluded. However, there remains a large group of persons whose personality deviations have been maintained from early life and who do not fall under any of the specific categories aforementioned, according to present diagnostic criteria, and yet who deviate significantly in their personality adjustment. The tendency to emphasize the psychogenic etiologic aspects to the exclusion of genogenic, histogenic and chemogenic factors has led some authorities to change the diagnostic term for the defect presented by these persons to "neurotic character." [6] Unfortunately, consideration of the psychogenic factors does not completely solve the problem presented by such patients, although much pertinent information has been obtained, but simply emphasizes one of the many etiologic aspects involved.

The occurrence of a high incidence of abnormal electroencephalograms in this group presents one avenue of study to the manifold relationships. Gerard and Libet [7] stated that the electrical

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1. Knott, J. R., and Gottlieb, J. S.: The Electroencephalogram in Psychopathic Personality, Psychosom. Med. **5**:139-141, 1943.

2. Hill, D., and Watterson, D.: Electroencephalographic Studies of Psychopathic Personalities, J. Neurol. & Psychiat. **5**:47-65, 1942.

3. Silverman, D.: Clinical and Electroencephographic Studies on Criminal Psychopaths, Arch. Neurol. & Psychiat. **50**:18-33 (July) 1943.

4. Maughs, S.: A Concept of Psychopathy and Psychopathic Personality: Its Evolution and Historical Development, J. Crim. Psychopath. **2**:329-356 and 465-499, 1941.

5. Preu, P. W.: The Concept of Psychopathic Personality, in Hunt, J. M.: Personality and the Behavior Disorders, New York, The Ronald Press Co., 1944.

6. Alexander, F.: The Neurotic Character, Internat. J. Psychoanal. **2**:292-311, 1930.

7. Gerard, R. W., and Libet, B.: The Control of Normal and "Convulsive" Brain Potentials, Am. J. Psychiat. **96**:1125-1152, 1940.

pulsations in the brain which determine the rhythm arise as the result of synchronized activity of the individual neurons. Abnormalities consist of a decrease or an increase in these pulsations outside a given range of frequency and amplitude. Psychologic activity may alter the basic normal rhythm temporarily, but so far as is known it does not give rise to any permanent change in rate or amplitude. Permanent or relatively long-lasting activity outside normal limits has been ascribed only to factors of inheritance, injury or infection of the brain and disturbances of cerebral metabolism. Hence the occurrence of such activity most probably indicates an abnormality in the neurophysiology of the cerebral cortex which may be expressed in terms either of synchronization or of individual neuron beat, and correlations may be sought between the electroencephalogram and the behavior in an attempt to cast light on a wider range of etiologic factors pertinent to the behavior. Such is the purpose of the present study.

METHOD

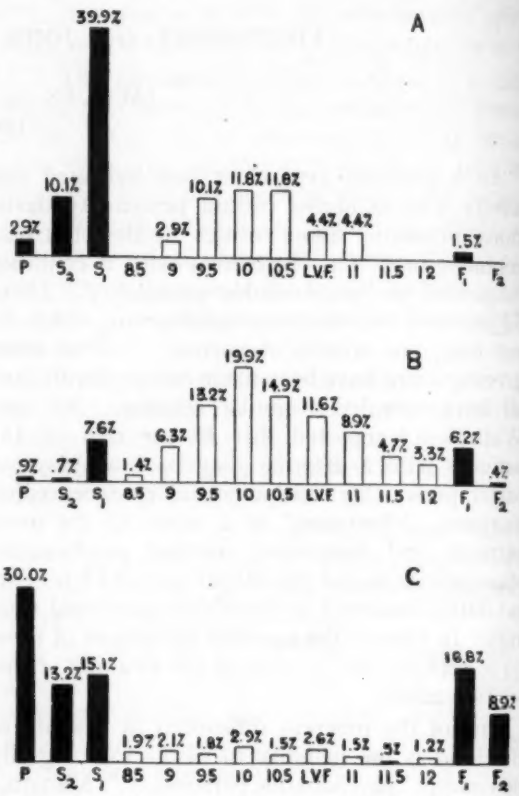
Six lead electroencephalograms were recorded from the 68 patients studied in this series. The monopolar method was used, and electroencephalograms were secured from the occipital, motor and frontal areas of each side with standard amplifiers and an ink-writing oscillograph. All records were taken for at least eighteen minutes.

In order to quantify the data, the scale of classification of Gibbs, Gibbs and Lennox [8] was employed. This method of classification has several advantages: It is possible to obtain a rapid estimate of the type; the classification is based on a single dimension, that of frequency, and the distribution of the various electroencephalographic types has been computed by Gibbs and associates from a sample of 1,000 neurologically screened normal subjects. The scale is shown in figure 1 of their article.[8]

The correspondence between the ratings made by one of us (J. R. K.), who secured and analyzed all the records, and the ratings of Dr. F. A. Gibbs was obtained by a rereading of records which he loaned us. The agreement was 97 per cent. In no case was there disagreement with respect to classification within the normal or the abnormal range, the nonagreement occurring only with respect to classification within the normal frequency limits and involving half-cycle frequencies.

The patients used in this study were carefully chosen on the basis of the completeness of the psychiatric, neurologic, physical and psychometric examination and the social history. In all cases the histories were given by the parents, a relative or some person who knew the patient well. The majority of the histories were corroborated by outside investigation.

From the social histories we chose a number of factors which we had previously found [9] to be important in establishing relations with the electroencephalographic records. These factors fell under two heads: the family history and a personal history of illness or injury. The family history was called positive if there was clear ancestral evidence of (1) psychosis, (2) maladjusted personality, (3) alcoholism or (4) epilepsy. The factors in the personal history of the patient which were chosen as significant included (1) premature birth, (2) birth injury or possible birth injury, (3) anoxia at birth or after birth, (4) injury to the head resulting in prolonged unconsciousness or delirium, (5) severe febrile illness complicated by delirium and (6) convulsions in infancy. With none of the patients was it suspected that the personal history of illness or



A, percentage distribution of electroencephalographic types for 68 patients with a condition diagnosed as psychopathic personality. At the bottom of each graph, *P* (paroxysmal) includes the various seizure discharges, the first three and the last two strips in figure 1 of Gibbs and associates [8]; S_2 indicates very slow activity; S_1, slightly slow activity; *LVF*, low voltage fast activity; F_1, slightly fast activity, and F_2, very fast activity. Categories shown in black are considered abnormal. The numbers indicate the percentages of the total series. *B*, percentage distribution of electroencephalographic types for 1,000 adult controls. The symbols are the same as those in *A*. *C*, percentage distribution of electroencephalographic types for 660 adult epileptic patients. The symbols are the same as those in *A*.

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50**:111-128 (Aug.) 1943.

9. Gottlieb, J. S.; Knott, J. R., and Ashby, M. C.: An Electroencephalographic Evaluation of Primary Behavior Disorders in Children, Arch. Neurol. & Psychiat., to be published.

injury played a part in the current difficulties of behavior. All patients who had positive neurologic signs or for whose personality variations it seemed likely that previous illness or injury could be held responsible were excluded at the outset of the investigation.

No records obtained during or after hyperventilation were used.

DATA

The distribution of the electroencephalograms of the 68 patients, classified according to the scale of Gibbs, Gibbs and Lennox, is shown in the figure, *A*. This distribution may be compared with that for 1,000 normal controls (figure, *B*) and that for 660 adult epileptic subjects (figure, *C*), recorded by them.[8]

The figure clearly indicates a difference in the form of the distribution curves for these three groups of subjects. The distribution for the psychopathic personalities was radically different than that for the epileptic adults, a fact which suggests that these two clinical groups represent two different electroencephalographic populations. Both differ from the neurologically normal electroencephalographic population. Twenty-seven (73 per cent) of the 37 patients had abnormal records classified as slightly slow (S^1) ("moderate amount of activity slower than 8.5 per second in any lead" [8]).

In further treatment of the data, records falling outside the normal range of frequencies (8.5 to 12 per second, and including low voltage fast activity) were called "abnormal," and in all statistical evaluations that unit was compared with the "normal" (all frequencies so covered in the Gibbs scale).

Table 1 presents an analysis of the electroencephalograms in relation to age and sex. With respect to age no statistically significant difference appeared, and it may be assumed that this variable was unrelated to the abnormalities in our sample. Forty-four of the patients were males, a ratio of approximately 2 to 1. The differences in the distributions of normality and abnormality with relation to sex, however, were not statistically significant, and one need not reject the hypothesis that the electroencephalographic patterns show no significant sex difference.

Table 2 presents an analysis of the electroencephalograms with relation to antecedent illness, injury and/or family history. Thirty-three patients (48 per cent) had a positive family history; 11 patients (16 per cent) had a history of antecedent illness or injury uncomplicated by a positive family history; 6 patients (9 per cent) had both a positive family history and a significant antecedent illness or injury, and 18 patients (27 per cent) had a negative family history and no antecedent illness or injury. Perhaps the most striking difference was that between the patients with a negative family history and no history of antecedent illness or injury and the patients with both a positive family history and a history of antecedent illness or injury. Of the former, 12 (67 per cent) had normal and 6 (32 per cent) abnormal

TABLE 1.—*Analysis of the Electroencephalogram* with Relation to Age and Sex*

	Male					Female					
Ages, Yr.	P	S^2	S^1	N	F^1	P	S^2	S^1	N	F^1	Totals
16-17	..	2	6	4	..	..	1	2	3	..	18
18-19	..	..	2	1	..	..	1	1	1	..	6
20-21	..	..	1	1	1	1	..	2	..	..	6
22-23	..	1	..	..	..	..	1	1	..	..	3
24-25	1	..	3	..	..	..	..	..	1	..	5
26-27	..	..	1	4	..	..	..	..	2	..	7
28-29	..	..	..	1	..	..	..	..	..	..	1
30-34	..	..	1	5	..	..	1	..	1	..	8
35-39	..	..	1	2	..	..	..	1	..	..	4
40-44	..	..	1	1	..	..	..	2	1	..	5
45-49	..	..	..	1	..	..	..	..	1	..	2
50-54	..	..	1	1	..	..	..	..	..	..	2
55-59	..	..	..	..	..	..	..	..	..	..	..
60 and older	..	..	1	..	..	..	..	..	..	..	1
	1 (2%)	3 (7%)	18 (41%)	21 (48%)	1 (2%)	1 (4%)	4 (17%)	9 (37%)	10 (42%)		68

* In accordance with the Gibbs classification, in this table and in table 2, P indicates paroxysmal; S^2 great amount of activity slower than 8½ per second in any lead; S^1, moderate amount of activity slower than 8½ per second in any lead; F^1, moderate amount of activity faster than 12 per second, and N, normal activity.

TABLE 2.—*Analysis of the Electroencephalogram with Relation to Antecedent Severe Illness or Head Injury and Positive Family History*

	Electroencephalograms				
	P	S^2	S^1	N	F^1
Positive family history only	..	5 (15%)	14 (42%)	14 (42%)	..
Illness or injury only	..	1 (9%)	6 (54%)	4 (36%)	..
Positive family history and illness or injury	1 (17%)	..	3 (50%)	1 (17%)	1 (17%)
No positive family history or illness	1 (5%)	1 (5%)	4 (22%)	12 (67%)	..
Totals	2 (3%)	7 (10%)	27 (40%)	31 (46%)	1 (1%)

electroencephalograms, while of the latter, 5 (83 per cent) had abnormal electroencephalograms and only 1 (17 per cent) had a normal electroencephalogram. When this difference in the distribution of abnormalities was treated with the chi square (χ^2) test, it was found that the difference was significant between the levels of confidence of 5 and 2 per cent. Therefore, one may reject the hypothesis that the difference between the distributions was due to chance.

TABLE 3.—*Analysis of the Electroencephalogram with Relation to a Positive Family History*

Family History	Electroencephalograms	
	Abnormal	Normal
Psychosis only	3	1
Psychosis and maladjusted personality	1	5
Psychosis and alcoholism	..	3
Psychosis and epilepsy	1	..
Totals	5	9
Maladjusted personality	9	4
Maladjusted personality and psychosis	1	5
Maladjusted personality and alcoholism	3	..
Maladjusted personality and epilepsy	2	..
Totals	15	9
Alcoholism	4	2
Alcoholism and psychosis	..	3
Alcoholism and maladjusted personality	3	..
Totals	7	5
Epilepsy	1	
Epilepsy and psychosis	1	
Epilepsy and maladjusted personality	2	
Total	4	

When the distribution of abnormalities for the patients with a completely negative history were compared with the distributions for the patients who had only a positive family history, it was found that the chi square test yielded a level of confidence of approximately 10 per cent. This suggests that the difference in the distribution may not be the result of chance factors, although the hypothesis needs further test. When the factor of illness and injury alone was studied and the distributions of electroencephalograms for patients with a positive history were compared with the distributions for the patients with a negative history, the chi square test yielded, again, a level of significance of approximately 10 per cent. Again, one may merely conclude that the probability that this difference in the distributions was due to chance is not great, but one needs further data for confirmation. Apparently, therefore, when the two factors of the family and of the personal history operate together, the differences are more reliable than when the factors operate separately.

Since there seems to be a relation between the factors which we have investigated and the abnormalities in the electroencephalograms, it becomes pertinent to break down our concept of a positive family history into its component factors (table 3) and to break down our concept of antecedent illness and injury into its component parts (table 4).

From a study of table 3 one can surmise that the factors of maladjusted personality and epilepsy are probably of greater importance in relation to the abnormal electroencephalogram than are the factors of psychosis and alcoholism, for the ratios of abnormal to normal electroencephalograms in the first two categories are essentially 2 to 1.

It is impossible to tell from table 4 whether any one factor of illness or injury is of greater importance than another because the number of cases in each category is too small.

COMMENT

In another study on the relation of the electroencephalographic pattern and primary behavior disorders in children,[9] the data strongly suggested that abnormal electroencephalograms were obtained for a high percentage of patients who had either a positive family history or a history of antecedent illness or injury, and for a significantly smaller percentage of patients for whom neither factor appeared. These results are consistent with the data reported here for the relation of the electroencephalogram to the psychopathic personality. The hypothesis, then, seems warranted that the abnormality evident

TABLE 4.—*Analysis of the Electroencephalogram with Relation to Illness and Injury*

Illness and Injury	Electroencephalograms	
	Abnormal	Normal
Prematurity	..	1
Prematurity and head injury	1	
Totals	1	1
Birth injury	1	..
Birth injury and convulsions	..	1
Totals	1	1
Head injury	1	1
Head injury and prematurity	1	..
Head injury and convulsions	1	..
Totals	3	1
Severe illness	5	2
Convulsions	1	..
Convulsions and birth injury	..	1
Convulsions and head injury	1	..
Totals	2	1
Anoxia (carbon monoxide poisoning)	1	
Birth injury and anoxia	1	

in the electroencephalograms either is inherited as such or is due to illness or injury in childhood which altered the function of cerebral tissue, yet was considered of no clinical significance. The suggestion follows, then, that the category "psychopathic personality," like the category of primary behavior disorders in children, may be further divided into (1) psychopathic personality with normal electroencephalogram and (2) psychopathic personality with abnormal electroencephalogram, the latter being further divisible into a type in which the electroencephalographic abnormality is of genetic origin and a type in which it is related to the cortical damage sustained early in life through illness or injury. It may further be suggested that the genogenic, chemogenic and histogenic factors are of greater etiologic importance than had heretofore been commonly ascribed to them.

Although this hypothesis seems warranted on the basis of the accumulated data, there remain several factors which may complicate it. An abnormal electroencephalogram is not pathognomonic of either psychopathic personality or primary behavior disorders in children, as is easily evident from the electroencephalographic examination of any psychiatric or neurologic population. With various other clinical entities there are associated abnormal waves, although apparently in a lower proportion than with the types of psychopathic personality reported on here, with the exception of epilepsy and known organic entities. It follows, therefore, that the presence of an abnormal electroencephalogram is not indicative of a specific type of deviation of behavior (for example, aggressiveness has been claimed by some investigators [2]), but is merely indicative of an apparently reliable probability that there will be some kind of deviation in behavior.[10] Furthermore, there are persons generally conceded to be "normal" who show general electroencephalographic characteristics falling beyond the present concept of normality. One might wonder whether the "normal" adjustment of these persons is true or superficial and whether there may in their future be periods of non-normal adjustment.

A likely formulation of these facts suggests that electroencephalographic abnormality (unless it is specific for the epilepsies) is merely an indication of an organism's susceptibility to difficulties in behavioral adjustment. Such persons may possess less elasticity in their neural limits [9] for withstanding the stresses and strains of the adjustment process, their neural limits varying but being dependent on genogenic, histogenic and/or chemogenic factors. It is probable that a significant proportion of the categories of psychopathic personality and primary behavior disorders in children are characterized by neural limits which lead to greater susceptibility, and hence to poorer adaptation in the patient's interreaction with the social environment. Whether there are any specific entities within these groups remains to be determined.

CONCLUSIONS

1. Fifty-four per cent of a series of 68 patients with a condition diagnosed as psychopathic personality, for which no organic cause was suspected, had abnormal electroencephalograms, characterized principally by the presence of slow or very slow waves.

2. When the electroencephalograms were classified according to the Gibbs, Gibbs and Lennox [8] scale and compared with the electroencephalograms of their groups of neurologic normal controls and epileptic patients, the distribution for the patients with psychopathic personality was radically different from the distributions for the other two populations.

3. Age and sex were unrelated to electroencephalographic abnormality.

4. Significantly greater proportions of abnormal electroencephalograms were found when there were both a positive family history (of psychosis, maladjusted personality, chronic alcoholism or epilepsy) and a personal history of cerebral trauma or severe illness than when neither of these factors was present. The statistical significance was not so great when only one of these factors was operating. However, the higher incidence of abnormal electroencephalograms associated with any one of these factors was probably not due to chance.

Dr. F. A. Gibbs loaned us samples of his electroencephalographic records, so that his evaluations could be compared with ours, and granted us permission to use his data on normal controls and epileptic patients.

10. In a preliminary attempt to correlate certain personality characteristics and the electroencephalographic pattern, we were unable to discover any significant relation. Regardless of the dominant traits, abnormalities were about equally distributed in the trait groups. Yet if only one characteristic had been chosen for study in a highly selected population, and electroencephalograms had been studied in relation to the presence or absence of the trait, it might have been possible to demonstrate such a relation, especially if that trait had entered into the definition of the population.

INTRACRANIAL PRESSURE IN THE HUMAN SUBJECT AT ALTITUDE

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It has been specifically stated by various authorities that there is an increase in the intracranial pressure at high altitudes. In view of this assumption, it was proposed to study the effects of altitude on the intracranial pressure in a patient with a large cranial defect. The subject owes his life to the fact that, with dura torn and cerebral substance protruding from the wound, he was fortunate enough to be transported by air to a hospital for specialized neurosurgical treatment. The tremendous size of the cranial defect which resulted and the fact that there was no retraction of the scar made direct and unusual instrumental observations possible. There are conflicting reports in the literature concerning the behavior of intracranial pressure at high altitudes when the subject is breathing oxygen and when he is anoxic. Walsh [1] described the case of a patient with a cranial defect following craniotomy in whom decompression on elevation to an altitude of 28,000 feet (16,900 meters) while he was breathing oxygen resulted in herniation of the overlying scalp to the extent of 1 cm. Walsh and Boothby [2] described an increase of intracranial pressure of about 30 mm. of water on decompression in human subjects breathing oxygen on their being subjected to altitudes of 30,000 feet (18,100 meters). Armstrong,[3] using goats, recorded the cerebrospinal fluid pressure on decompression with cisternal punctures and observed that there was an increase in pressure which began at an altitude of 18,000 feet (10,880 meters) and continued up to an altitude of 50,000 feet (30,240 meters). In his experiments he failed to mention the presence of abdominal distention and its influence on intracranial pressure through the increased venous pressure. He recorded an increase amounting to "several inches of water pressure." Bergeret and Giordan,[4] working with dogs, showed increases in intracranial pressure, as well as in venous pressure, when the animals were subjected to simulated high altitudes, and these changes could be reversed by the giving of oxygen, although the altitude was maintained.

Walsh, Walsh and Boothby and Armstrong all reported the appearance of bubbles in the column of fluid filling the manometer on ascent to high altitudes.

CLINICAL REPORT OF A CASE

The patient was accidentally shot when a Sten gun, which he was replacing on the floor, went off. The bullet, at this close range, entered the head just above the left eyebrow and made its exit just over the vertex. The patient was instantly unconscious and could not recall details of the accident. The trauma occurred about thirty-six hours prior to his admission to the hospital.

He was transferred from Nova Scotia, where the shooting occurred, by means of two aircraft, additional short distances being covered by rowboat, truck and ambulance. Because of the severe loss of blood he received two transfusions of plasma in isotonic solution of sodium chloride (500 cc. each) in preparation for transportation. Also, he was given morphine sulfate, ¼ grain (16 mg.), at the beginning of the flight. Evacuation by air was undertaken at an average alti-

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Investigations carried out for the Associate Committee on Army Medical Research, National Research Council, Ottawa, and the Research Division, Director General of Medical Services, National Defense Headquarters, Ottawa, Canada.

1. Walsh, M. N.: Changes in Intracranial Volume on Ascent to High Altitudes and Descent as in Diving, Proc. Staff Meet., Mayo Clin. **16**:220, 1941.

2. Walsh, M. N., and Boothby, W. M.: Demonstration of Air Bubbles in Spinal Fluid Under Lowered Atmospheric Pressures Produced in a Low Pressure Chamber, Proc. Staff Meet., Mayo Clin. **16**:225, 1941; correction, ibid. **16**:304, 1941.

3. Armstrong, H. G.: Aviation Medicine, Baltimore, Williams & Wilkins Company, 1939.

4. Bergeret, P., and Giordan, P.: The Cerebrospinal Fluid Pressure Under the Influence of Atmospheric Depression, J. de physiol. et de path. gén. **36**:1050, 1938.

tude of 6,000 feet (3,600 meters). No ill effects due to the flight were observed, and the pulse was recorded as averaging 110 per minute.

Examination on his arrival at the hospital revealed a penetrating wound of the left frontal region of the skull, with tearing of the dura and cerebral laceration. He was very pale and obviously was suffering from the effect of hemorrhage. The red blood cell count was 3,790,000. Clinically, there was right hemiplegia, with

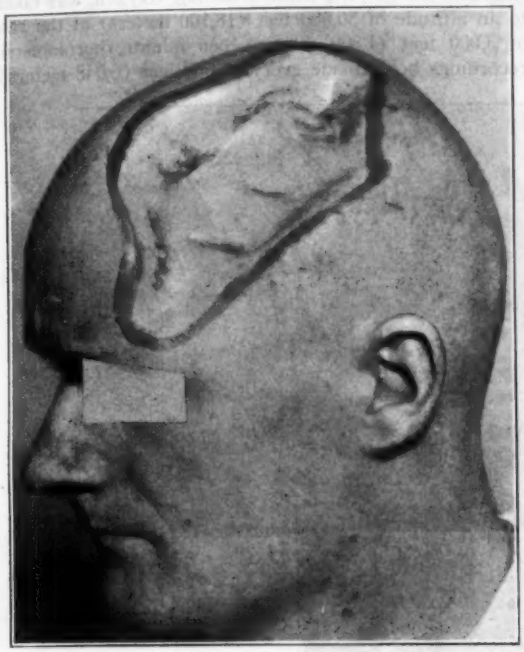

Fig. 1.—Cranial defect outlined to show its extent.

the characteristic reflex changes. The right ear drum was bulging, and there was bluish discoloration of the tympanic membrane.

Damage to the brain and skull was extensive. There was much pulped brain tissue, and large blood clots outlined the bullet's path. Bits of metal and fragments of bone were present in the softened brain. The calvarium was extensively comminuted. Above the wound of entrance, which was cleancut, there was an irregular laceration of the scalp, through which a fragment of bone had apparently been blown. Over the wound of exit, which was large, the laceration of the scalp was wide and irregular.

The damage to the brain extended back beyond the central fissure; though the injury extended deep in the cerebral substance, the ventricle was not opened.

At operation, which was performed immediately on his admission, the scalp and skull were completely debrided, and softened brain substance was irrigated away. Blood clots were also removed. The dura was closed loosely, and a rubber dam drain, brought out by means of a stab wound, was left in the defect made by removal of the damaged brain substance.

An encephalogram made four and a half months later showed that the skin overlying the defect moved out considerably when the ventricles were being filled, and the defect for some time afterward was considerably fuller.

At the time of the present investigation the defect, which measured approximately 16 by 10 by 2.5 cm., was perfectly healed and freely mobile under stresses of artificially increased intracranial pressure (fig. 1).

METHOD OF INVESTIGATION

Decompression Chamber.—A decompression chamber capable of accommodating twelve persons was used throughout the experiments. Preliminary decompression was carried out with a view to familiarizing the subject with the knack of maintaining the patency of the eustachian tubes and to acquainting him with the unusual surroundings of the chamber, in order to reduce emotional upset to a minimum.

Herniometer.—The light cerebral herniometer constructed consisted of a rubber cylinder, graduated in millimeters, which moved freely through a plastic guide (fig. 3). The apparatus was fixed to the subject's head by means of rubber cement.

The efficiency of the apparatus was tested by various methods which raise the intracranial pressure, with the following readings: (*a*) normal oscillation due to pulsation of the defect, 1 mm.; (*b*) with the patient firmly gripping an object, 3 mm.; (*c*) with the subject "bearing down," 4 mm.; (*d*) with the subject laughing, 5 to 6 mm.; (*e*) with application of a small sphygmomanometer cuff to the neck at a pressure of 90 mm. of mercury, 8 mm., and (*f*) with a postural change of 90 degrees (from 30 degrees feet down to 60 degrees head down) on the x-ray table, 15 mm.

Cranial Plethysmograph.—A plaster cast of the cerebral defect and the surrounding cranium was made, and from it an exact stone copy was constructed. A Plexiglass dome was formed by stretching Plexiglass under steam heat. The principle adopted was to clamp the

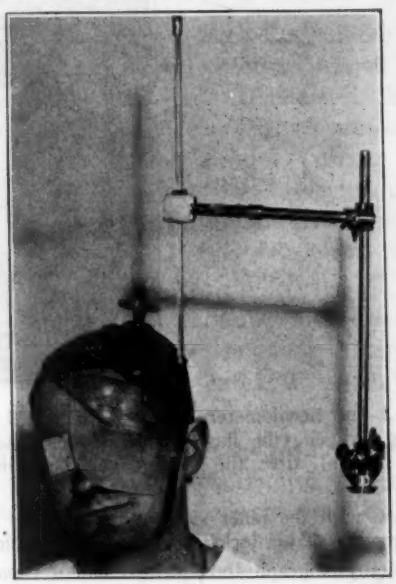

Fig. 2.—Cranial plethysmograph cemented and strapped in position.

Plexiglass firmly on to an iron frame, place the replica of the skull (with defect filled), and with considerable weight on it, vertex downward on the tray thus formed and subject the whole to steam heat at approximately 230 F. The mold obtained was trimmed and drilled for the insertion of manometer connections. A female stone mold was also constructed to prevent any possible loss in shape. Brass manometer insertions were made and sealed flush into the Plexiglass with heat. The rigid

skull prosthesis was fixed to the patient by means of rubber cement, firmly held in position by means of rubber straps and filled with water, which had previously been boiled. The most dependent outlet was connected to a 2 mm. bore manometer, graduated in centimeters, and the other outlet, to a piece of clamped rubber tubing. Great care was taken to prevent the entrance of any bubbles of air and to obtain a perfect water-tight seal. Certain difficulties were encountered in the construction of this apparatus—a water-tight seal demanded that the Plexiglass dome should be of perfect fit, and special attention had to be paid to the area over the left eye, where a thin rubber dam was cemented to the inner side of the dome; the brass manometer outlets were formed was held in position with a rubber strap. A couch was arranged transversely across the decompression chamber; a lumbar puncture was made with an 18 gage needle between the third and the fourth lumbar vertebra, and the needle was connected with a manometer.

With the aforementioned apparatus, experiments in the decompression chamber were carried out as follows:

EXPERIMENT 1: The herniometer was fixed in position, and the subject, while breathing oxygen, was taken to an altitude of 30,000 feet (18,100 meters) at the rate of 3,000 feet (1,800 meters) per minute, herniometric recordings being made every 10,000 feet (6,048 meters).

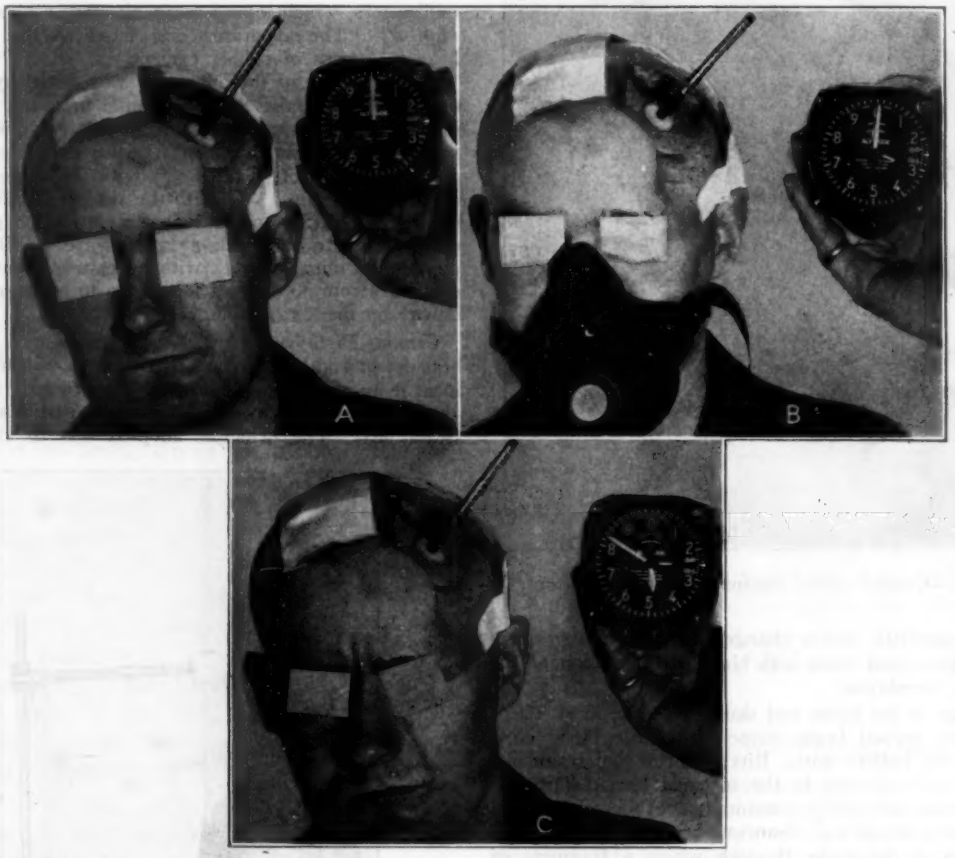

Fig. 3.—*A*, herniometer at ground level; *B*, herniometer at 30,000 feet (18,100 meters), with the subject breathing oxygen (the flash bulb exploded when this picture was taken), and, *C*, herniometer at 25,000 feet (15,320 meters) after the subject had been deficient in oxygen for two minutes and twenty seconds.

sunk flush with the inner side of the dome to prevent the occurrence of air locks around their shoulders.

The plethysmograph thus formed had a capacity of 203 cc. and, because of such a volume of fluid, transmitted impulses with great accuracy (fig. 2).

The efficiency of the apparatus was tested by various methods, with the following results: (*a*) with normal oscillations, 55 mm. of water systolic and 75 mm. diastolic; (*b*) on the subject's coughing, 35 mm. systolic and 180 mm. diastolic; (*c*) on his laughing, 35 mm. systolic and 150 mm. diastolic, and (*d*) with light gripping of an object, 45 mm. systolic and 220 mm. diastolic.

Lumbar Puncture.—The cerebral defect was filled completely with rapidly setting plaster, and the cast so

The pressure in the decompression chamber was then dropped to simulate the pressure at 25,000 feet (15,320 meters), and the subject's mask was removed for two minutes and twenty seconds. Descent to ground level was then made, at the rate of 1,000 feet (604 meters) per minute. Photographic recordings of the herniometric readings were obtained at ground level, at 30,000 feet (18,100 meters) while the patient was taking oxygen and at 25,000 feet (15,320 meters) when he was anoxic (fig. 3).

EXPERIMENT 2: With the plethysmograph in place, an ascent to 25,000 feet (15,320 meters) was made with the subject breathing oxygen and in a sitting posture (fig. 2). He remained at this altitude for twenty minutes, and during that time his oxygen mask was removed on

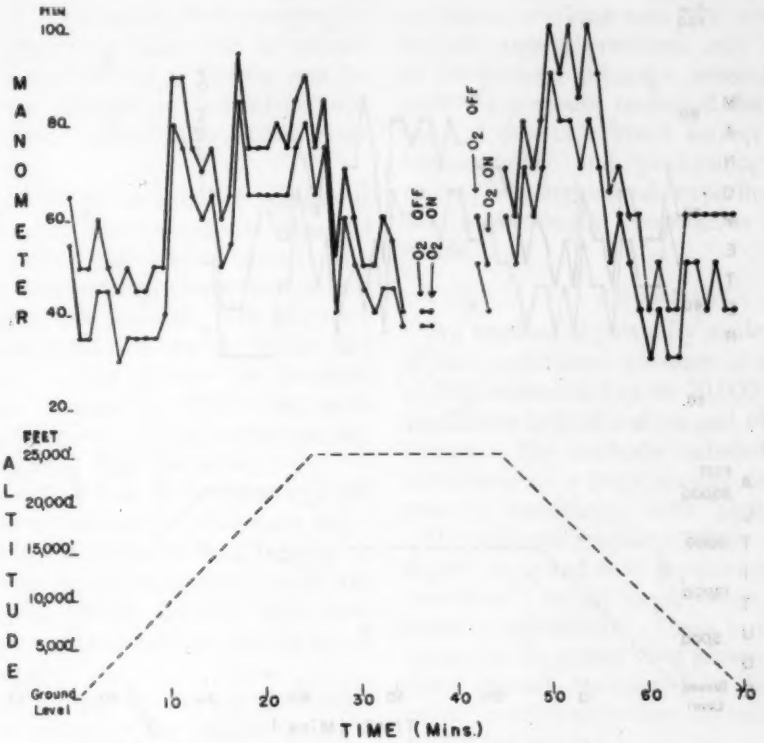

Fig. 4.—Manometric readings taken while the patient (sitting) was breathing oxygen except for two short exposures to anoxia.

two occasions, for sixty and seventy seconds respectively. Manometric readings (maximum and minimum oscillations) were taken every minute. The ascent and descent were made at the rate of 1,000 feet (604 meters) per minute.

EXPERIMENT 3: Again, with the plethysmograph in position, ascent to 15,000 feet (9,000 meters) was made without oxygen and with the subject in a comfortable reclining position. He remained at this altitude for twenty minutes, after which a further ascent to 20,000 feet (12,000 meters) was made, where he remained for ten minutes. Oxygen was then administered and descent to ground level effected. The ascent and descent were made at the rate of 1,000 feet per minute.

EXPERIMENT 4: After insertion of the lumbar puncture needle and its connection with the manometer, and while the patient was breathing oxygen, ascent was made to 30,000 feet (18,100 meters) at the rate of 3,000 feet (1,800 meters) per minute, and manometric readings were made each minute. After nine minutes at an altitude of 30,000 feet, the chamber was lowered to 20,000 feet (12,000 meters), and the oxygen mask was removed for sixteen minutes, after which it was replaced. Descent to ground level was made at the rate of 1,000 feet (604 meters) per minute. Throughout the experiment manometric readings were noted every minute except after replacement of the oxygen mask, when thirty second readings were taken. The efficiency of the manometer was checked by tests for patency (deep respiration, pressure on the jugular veins and talking).

INTERPRETATION OF RESULTS

EXPERIMENT 1.—In efficiency trials the herniometer was shown to reflect with reasonable sensitivity any changes occurring in the intracranial pressure. Direct observations and photographic recordings (fig. 3) showed that no significant changes in intracranial pressure occurred with increased altitude (up to 30,000 feet) when the subject was breathing oxygen or was in the acutely anoxic state (exposure of two minutes and twenty seconds at an altitude of 25,000 feet).

These results are contrary to the observations of Walsh on a patient with a cranial defect of relatively minor extent at an altitude of 28,000 feet.

This experiment proves conclusively that such a subject, contrary to reports from other investigators, could safely be evacuated by air at high altitude, and even in a slightly anoxic state.

EXPERIMENT 2.—This experiment showed that no changes of intracranial pressure, other than the alterations considered as normal variations, occurred when the subject was breathing oxygen at altitudes of as high as 25,000 feet and when acute anoxia was induced at this altitude (fig. 4). These plethysmographic observations confirm the herniometric readings in the previous experiment.

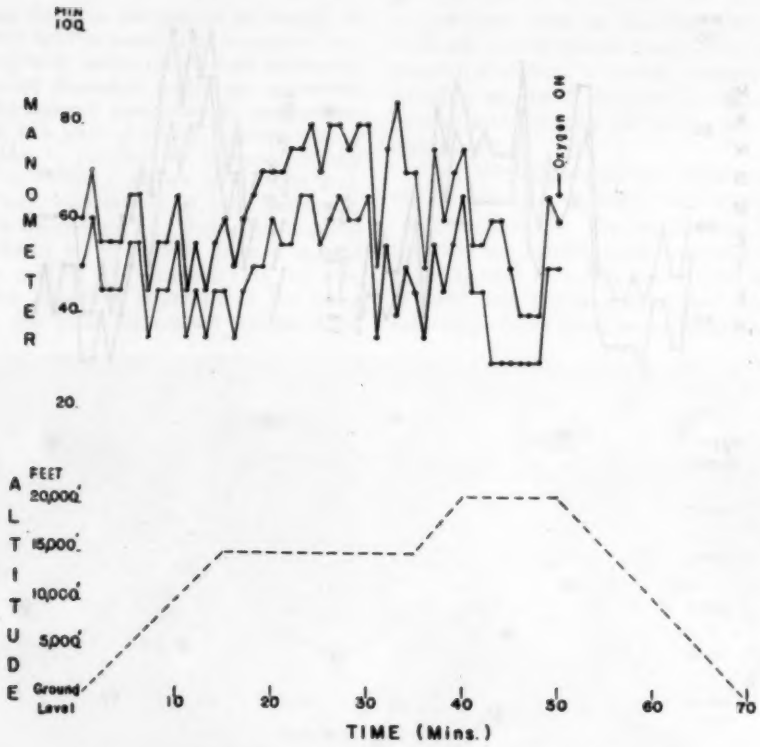

Fig. 5.—Exposure to anoxia (with patient resting and comfortable).

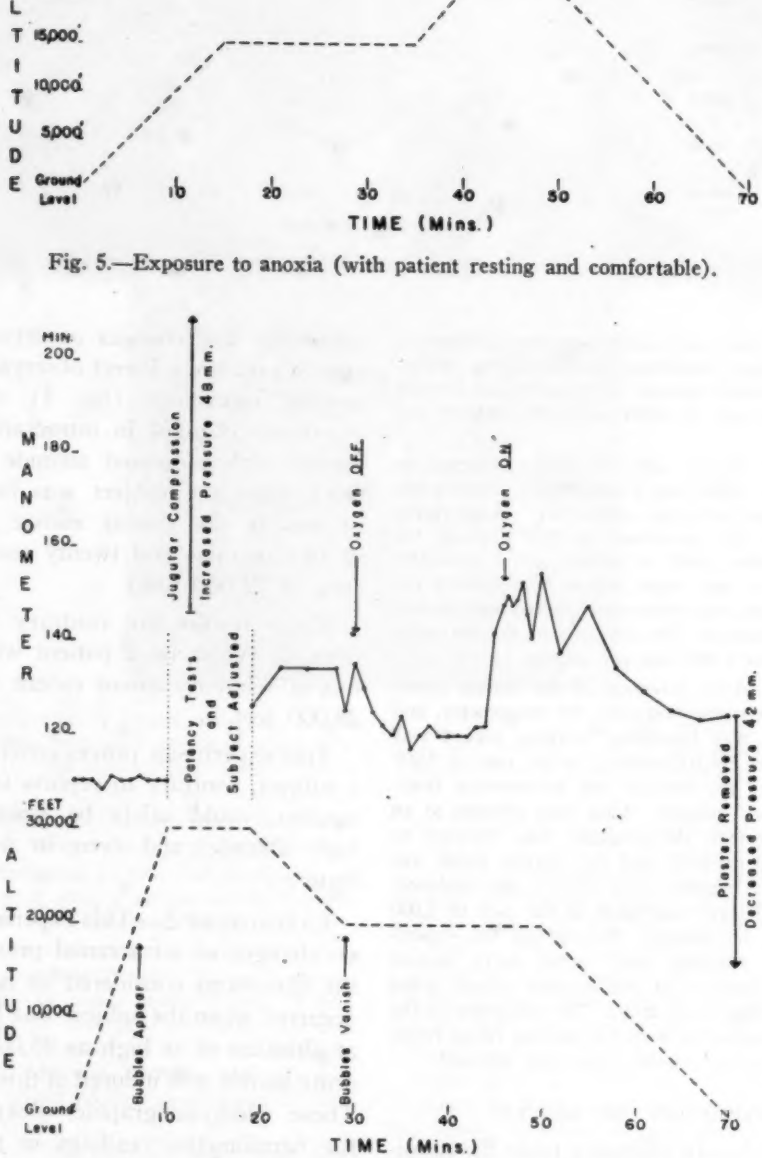

Fig. 6.—Cerebral spinal fluid pressures obtained by lumbar puncture.

EXPERIMENT 3.—The same plethysmographic technic was employed as that used in experiment 2, but a chronic degree of anoxia was induced. Again, no changes in the intracranial pressure other than normal fluctuations were noted (fig. 5).

EXPERIMENT 4.—The creation of conditions simulating those of an intact skull was arranged by completely closing the cranial defect with a freshly poured, quick-setting plaster cast, which was firmly strapped into position. The efficiency of such an arrangement was proved by the fact than on removal of the plaster the pressure dropped 42 mm. Ascent to 30,000 feet with the patient breathing oxygen did not cause any increase in the spinal fluid pressure.

Soon after an altitude of 20,000 feet (12,000 meters) was reached, minute bubbles were noted to be rising in the manometer and lodging in the meniscus; this observation agrees with the reports of Thorner, Walsh, Boothby and Armstrong, all of whom noted bubbles, but at somewhat lower altitudes.

At 30,000 feet the patency of the manometer was tested by pressing on the jugular veins, a procedure which increased the pressure by 48 mm.; the cardiac oscillations were 1 mm. and the respiratory excursions 4 mm.

The subject was brought down to an altitude of 20,000 feet, and his oxygen mask was removed for sixteen minutes, during which time clinical anoxia of a considerable degree was induced. An increase of only 23 mm. of spinal fluid pressure was recorded toward the end of this exposure, and there was no appreciable change in the pressure on administration of oxygen (fig. 6). Although this result is inconsistent with the observations of some investigators, White and associates, working with cats, noted that in some animals anoxia produced only slight elevations of intracranial pressure, whereas in other animals the pressure remained the same. The results of this experiment further corroborate the herniographic and plethysmographic observations. Throughout all experiments the subject was exceptionally cooperative and emotionally stable.

SUMMARY

An unusual opportunity made possible a study of the intracranial pressure in a human subject at high altitudes (up to 30,000 feet) and under conditions both of sudden and of more prolonged anoxia. The methods included (1) direct observations on a huge cranial defect; (2) herniometric recordings, with photographic check; (3) plethysmographic technic, and (4) recording of the spinal fluid pressure through a lumbar puncture. In all experiments the conclusions were in agreement: There is no significant increase in the intracranial pressure in man (other than normal variations) at high altitude and under conditions either of sudden or of more prolonged anoxia.

These results are regarded as of particular importance with respect to transportation of casualties and sick persons by air. Moreover, experience with other patients with head injuries indicates that these casualties tolerate air transportation well. In fact, it may be to them a life-saving measure by providing rapid, definitive treatment. Any specific contraindication bearing on changes in intracranial pressure is not in accord with the experimental and practical evidence obtained from the case just described.

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RELATION OF CIRCULUS ARTERIOSUS TO HYPOTHALAMUS AND INTERNAL CAPSULE

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In studies bearing on the blood supply of the brain, a number of authors have recently stressed the contributions of the circulus arteriosus to the hypothalamus.[1] In the present study, when the branches of the circulus were traced out (fig. 1), it was observed that many of them sent terminals into the depths of the brain to supply various areas of the internal capsule (fig. 2). This communication deals with several interesting observation made in the course of this study.

My method of approach in dissection of these arteries consisted in identifying a certain vessel of the circulus, following a particular twig peripherally until it disappeared within the brain substance and then, by carefully scraping away the overlying tissue, tracing the vessel to its termination.

It was found that fixed brains were better suited for this purpose than fresh brains since the brain substance was more crumbly, and therefore more easily removed. For example, with this method the recurrent artery (fig. 3), when identified as it came off from the anterior cerebral artery, at the level of the anterior communicating artery, was traced laterally and occipitally toward the region of the insula. The overlying cortex and white matter of the temporal, frontal and parietal operculums were removed. The cortex of the insula, together with the capsula extrema, was scraped away; the external capsule was lifted up with the handle of the scalpel, and the lenticular nucleus was exposed. The branches of the recurrent artery were then followed successively into the internal capsule by gently tugging at each respective branch and scraping away the overlying nuclear substance. This method is somewhat similar to that employed by Ayer and Aitken,[2] the difference lying in the use of fixed brains in this study, rather than the fresh specimens studied by these authors.

OBSERVATIONS

The observations to be reported are graphically presented in figures 1, 2 and 3. Figure 1 shows the various branches observed and traced; figure 2, the terminations in relation to the internal capsule, and figure 3, the distribution of the recurrent arteries, which seems not to have been indicated by other authors.[3] Heubner,[3a] of course, while describing a number of the branches of the anterior cerebral artery, did not refer to any as "Heubner's recurrent artery." Lesem[3b] failed to mention this vessel at all. De Almeida[3c] referred to "Heubner's artery," which he stated may at times arise from the middle cerebral artery. Grinker[4] spoke of the "recurrent artery of Heubner," without illustrating it and cited the work of Ayer and Aitkin,[2] who likewise did not illustrate its distribution.

The accompanying figures show the distribution of these arteries.

Anterior Cerebral Artery.—The anterior cerebral artery, which supplies the more cephalic hypothalamic area through its anterior medial ganglionic branches (fig. 1), also supplies the more cephalic part of the internal capsule, i. e., the anterior limb and the genu. This it does through recurrent branches, which arise from the lateral aspect of the parent trunk.

From the Alfred Ullman Laboratory for Neuropsychiatric Research.

1. Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects, Edinburgh, Oliver & Boyd, Ltd., 1938. Finley, K. H.: Angio-Architecture of Hypothalamus and Its Peculiarities, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:286, 1940. Foley, J. M.; Kinney, T. D., and Alexander, L.: The Vascular Supply of the Hypothalamus in Man, J. Neuropath. & Exper. Neurol. **1**:265, 1942. LeBlanc, E.: Les artères de la région infundibulo-tubérienne, Trav. du Lab. de anat., Alger, 1926, pp. 14-20. LeBlanc, E.: Les artères de la fosse interpédonculaire et de l'espace perforé postérieur, ibid., 1928, pp. 16-28. Rubinstein, H. S.: The Anterior Communicating Artery in Man, J. Neuropath. & Exper. Neurol. **3**:196, 1944.

2. Ayer, J. B., and Aitken, H. F.: Note on the Arteries of the Corpus Striatum, Boston M. & S. J. **156**: 768, 1907.

3. (*a*) Heubner, O.: Die luetische Erkrankung der Hirnarterien, Leipzig, F. C. W. Vogel, 1874. (*b*) Lesem, W. W.: The Comparative Anatomy of the Anterior Cerebral Artery, Post-Grad. M. J. **20**:455, 1905. (*c*) de Almeida Prado, F.: Notes on the Anterior Cerebral Artery, Rev. de med., São Paulo **16**:75, 1932.

4. Grinker, R. R.: Neurology, Springfield, Ill., Charles C Thomas, Publisher, 1934, p. 571.

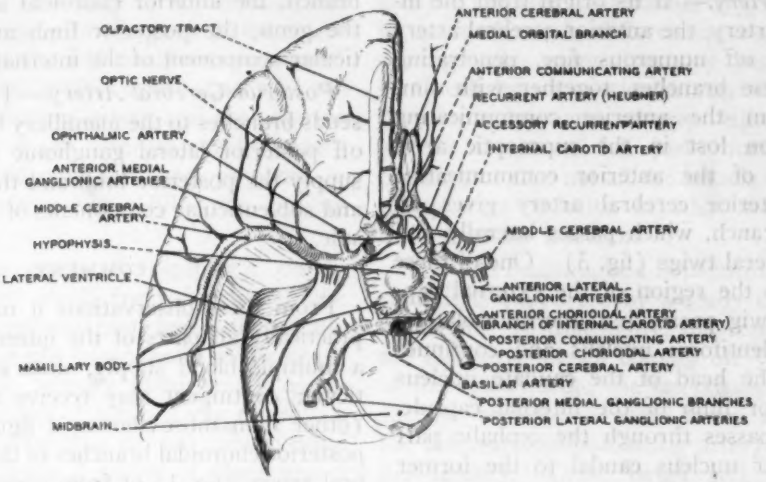

Fig. 1.—The arterial circle with its branches to the basal ganglia and the hypothalamus. Tuberal branches (not labeled) are given off from the right internal carotid artery.

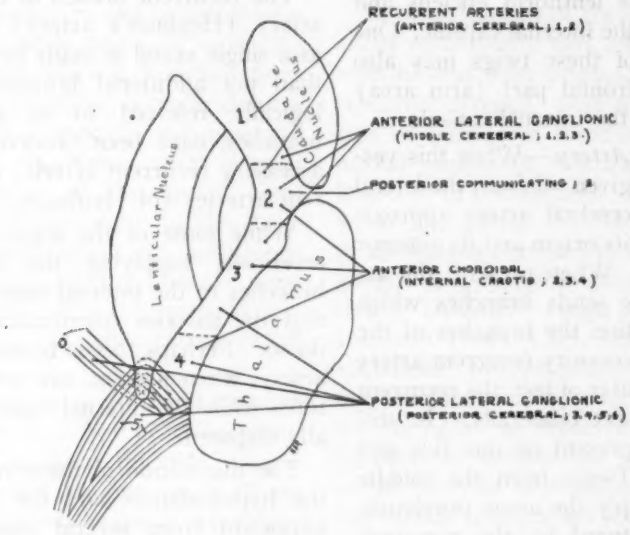

Fig. 2.—Diagram showing blood supply to various components of the internal capsule. Leaders and numbers indicate the parts supplied by the arteries (parent stems in parentheses).

The components of the internal capsule are designated as follows: *1* indicates the anterior limb (associative in function); *2*, the genu (motor fibers to the face); *3*, the anterior two thirds of the posterior limb (motor); *4*, the posterior third of the posterior limb (sensory); *5*, retrolenticular component (visual), and *6*, sublenticular component (auditory).

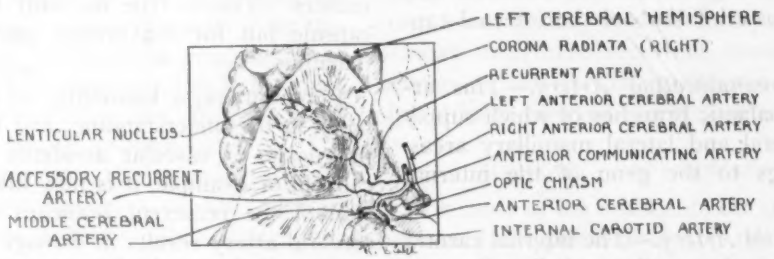

Fig. 3.—Dissection showing the recurrent and accessory recurrent arteries. The broken line branches indicate their penetration through the substance of the lenticular nucleus in order to reach the internal capsule.

Recurrent Artery.—At its origin from the internal carotid artery, the anterior cerebral artery (fig. 1) gives off numerous fine, penetrating branches. These branches, together with similar twigs from the anterior communicating artery, are soon lost in the supraoptic area. In the region of the anterior communicating artery, the anterior cerebral artery gives off its recurrent branch, which passes laterally and divides into several twigs (fig. 3). One of these twigs passes to the region of the external capsule; another twig passes into the anterolateral aspect of the lentiform nucleus and continues medially into the head of the caudate nucleus and the anterior limb of the internal capsule. Another twig passes through the cephalic part of the lenticular nucleus caudal to the former branch and can likewise be traced to the anterior limb of the internal capsule. Two or three small branches then penetrate the midregion of the lateral protuberance of the lentiform nucleus and continue to the genu of the internal capsule. One of the more occipital of these twigs may also extend into the more frontal part (arm area) of the posterior limb of the internal capsule.

Accessory Recurrent Artery.—When this vessel is present, it may be given off from the lateral aspect of the anterior cerebral artery approximately midway between its origin and its anterior communicating branch. When present, the accessory recurrent artery sends branches which may parallel in distribution the branches of the recurrent artery. The accessory recurrent artery is not constant. As a matter of fact, the recurrent artery, too, may be absent bilaterally. In still other brains it may be present on one side and absent on the other. Twigs from the middle cerebral artery then supply the areas previously described as being nurtured by the recurrent arteries.

Middle Cerebral Artery.—The middle cerebral artery, some of the anterior lateral ganglionic twigs of which reach the more lateral hypothalamic areas, sends well marked branches to the anterior limb, the genu and the anterior two thirds of the posterior limb of the internal capsule.

Posterior Communicating Artery.—This artery, the hypothalamic branches of which supply the lateral tuberal and lateral mamillary areas, also sends twigs to the genu of the internal capsule.

Internal Carotid Artery.—The internal carotid artery, which sends small, medially disposed branches (unlabeled in figure 1) to the optic chiasm, the infundibulum and the tuberal area, also sends a prominent occipitolaterally coursing branch, the anterior choroidal artery, to supply the genu, the posterior limb and the retrolenticular component of the internal capsule.

Posterior Cerebral Artery.—This artery, which sends branches to the mamillary bodies, also gives off posterior lateral ganglionic branches, which supply the posterior limb and the retrolenticular and sublenticular components of the internal capsule.

COMMENT

From these observations it may be seen that practically all parts of the internal capsule have a multiple blood supply, since even the sublenticular contingent may receive additional twigs (other than those shown in figure 2) from the posterior choroidal branches of the posterior cerebral artery (fig. 1) or from penetrating branches of the superior cerebellar artery as this vessel winds around the cerebral peduncle.

The recurrent branch of the anterior cerebral artery (Heubner's artery) has been observed as a single vessel in many brains, but more often than not additional branches, which could be logically referred to as accessory recurrent branches, have been observed (fig. 1). These accessory recurrent arteries reenforce the recurrent arteries (of Heubner).

While most of the segments of the circulus arteriosus supplying the hypothalamus send branches to the internal capsule, it is interesting that the anterior communicating artery fails to do so. Perhaps this is because the twigs of this artery, when present, are strictly midline structures while the internal capsules are more laterally disposed.

The disposition of these vessels in relation to the hypothalamus and the internal capsule is important from several standpoints. First, it shows that in spite of the dramatic, and in most instances tragic, cessation of function following gross cerebrovascular accidents, for the greater part of the patient's life prior to such an overwhelming upset nature has been bountiful in the multiple blood supply to many important nerve centers. This is true not only for the internal capsule but for the greater part of the hypothalamus.

Furthermore, a knowledge of this disposition helps in the understanding, and therefore in the prognosis, of vascular accidents observed clinically. For example, it is now known that occlusion of the recurrent branches of the anterior cerebral artery results in damage to the cephalic portion of the caudate and lenticular nuclei and to the intervening internal capsule. This results in facial and lingual paralysis (defect in the internal capsule) and rigidity (involvement of

the basal ganglia). Yet only by appreciating the quadruple blood supply to the genu of the internal capsule through the additional anterior lateral ganglionic branches (middle cerebral artery), the posterior communicating artery and the anterior choroidal branch of the internal carotid artery can one understand why the facial paralysis in most instances clears up while the rigidity persists.

While in most cases of hemiplegia purely motor disturbances result from damage to the anterior lateral ganglionic branches of the middle cerebral artery, one not infrequently sees a hemiplegic patient with sensory disturbances corresponding to the motor deficits. Only recently a colleague asked how such a clinical picture could be explained. Figure 2 makes it clear that a lesion involving the anterior choroidal artery may lead to just such a result.

Finally, it is helpful to remember the common source of the blood supply to the hypothalamus and to the internal capsule when one seeks an explanation of various visceral manifestations observed in cases of otherwise somatic defects. Ischemic changes have frequently been observed in the hypothalamus of patients with vascular accidents in other areas of the brain. Such changes not only may contribute to the vasomotor phenomena which affect the hemiplegic patient but may account for the hitherto inexplicable glycosuria and hyperproteinemia observed in some patients with acute cerebrovascular accidents.

The observations here reported are at variance in certain respects with those of Alexander.[5] This author, in his beautiful injection experiments, reported that the various areas of the basal ganglia and the internal capsule were completely dependent on specific and respectively single vascular sources. To the anterior limb and the dorsal part of the posterior limb of the internal capsule Alexander ascribed the striate arterioles; to the genu, the capsular branches of the internal carotid artery, and to the ventral part of the posterior limb and the retrolenticular component, the anterior choroidal artery. In this scheme, this author and I are in greatest agreement with respect to the anterior limb, since he derived his "striate arterioles" from both the anterior and the middle cerebral artery. The greatest difference relates to the genu to which area I have traced branches of the anterior cerebral artery, the middle cerebral artery, the posterior communicating artery (when present) and the anterior choroidal artery. It is difficult to reconcile such differences, especially since, even grossly, more than one vessel can often be traced into a particular zone of the internal capsule, unless one assumes either that Alexander's injections fell just short of sufficient pressure or that not all the vessels of a particular group were included in what was later taken to be a group injection.

The latter assumption is particularly engaging, since it is supported by a study of Alexander's figure 26. In this figure, the recurrent arteries are distinctly shown coming off (on either side of the brain) from the lateral aspect of the respective anterior cerebral artery at the level of the anterior communicating artery (unlabeled in his figure). These twigs and the accessory recurrent branches, when present, can usually be traced to the region of the anterior limb and the genu of the internal capsule.

In his injections of the striate branches, Alexander consistently tied off the anterior cerebral arteries near their origins, thereby excluding the recurrent arteries. One would assume therefore that he considered these branches foreign to the medial ganglionic vascular group (his "striate branches of the anterior cerebral artery"). Yet when Dr. James W. Ayer raised the question of anomalous branches to this region of the basal ganglia and referred specifically to the description of Heubner [5] (page 128), Alexander, in his response (page 130), admitted certain "minor variations" with reference to his figure 26. However, instead of identifying the unlabeled branches in this figure as recurrent arteries, he referred to them as components of the striate branches of the anterior cerebral artery (". . . entering striate arteries are derived from two large mainsprings originating from the anterior cerebral artery"). If Alexander meant to include these recurrent branches as part of the medial ganglionic vascular system, as he did in his response to Dr. Ayer, they should have been injected, together with the other twigs of this group. If, on the other hand, as one may judge from his excluding them from injection, he considered that these recurrent branches did not belong to the medial ganglionic group, they should have received independent attention.

SUMMARY AND CONCLUSIONS

In a study of the relation of the circulus arteriosus to the hypothalamus and the internal capsule, it was observed that in many instances a common parent stem supplies the hypothalamus and the internal capsule. All parts of the internal capsule are supplied by more than one source.

5. Alexander, L.: The Vascular Supply of the Strio-Pallidum, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:77, 1942.

The area of richest blood supply is the genu of the internal capsule.

Study of the recurrent branches of the anterior cerebral artery revealed that, in addition to the recurrent branch of Heubner, accessory recurrent arteries exist. These vessels, when present, parallel the distribution of the recurrent artery. [Correlations have been presented between the pathological involvement of the recurrent and anterior choroidal arteries and the respective clinical findings. In addition, discrepancies between injection experiments and dissectional methods of study have been considered and an attempt has been made to reconcile these differences.]

Concomitant vasomotor and visceral phenomena observed in cases of otherwise grossly somatic clinical defects incident to cerebrovascular accidents are explained on the basis of coincident ischemia of the hypothalamus.

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NEUROLOGIC COMPLICATIONS FOLLOWING THE USE OF CONTINUOUS CAUDAL ANESTHESIA

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Numerous investigators have previously demonstrated the value of caudal anesthesia in obstetrics, and the method has been recently modified and popularized by Hingson and Edwards and others. All have agreed that its use should be restricted to the specialist in adequately equipped hospital centers because of the possibility of serious complications. Continued study only will determine its ultimate value for more general use. We have recently had the opportunity of studying 2 cases with complications which have not as yet been encountered in the literature.

REPORT OF CASES

CASE 1.—A woman aged 26 had low forceps delivery of a normal living male infant, with repair of a left lateral episiotomy incision on Oct. 17, 1942. Caudal anesthesia was induced by the ureteral catheter technic, and 960 cc. of a 1.5 per cent solution of procaine hydrochloride was administered, at the rate of 20 cc. per hour. Delivery was slightly prolonged but uneventful. Localized pain over the lumbosacral region with bilateral sciatic radiation was noted shortly after parturition. There was also urinary retention, necessitating catheterization for a few days. There were analgesia in the right saddle area and hypesthesia to the level of the second lumbar segment on the right side and to the level of the fourth lumbar segment on the left side. The patient had pain on raising the straight leg, and the Lasègue sign was positive bilaterally at a flexion of 20 degrees. The reflexes were active and equal on the two sides.

Cystoscopic and retrograde pyelographic studies, on October 21, showed no calculi or evidence of pathologic process except for elongation of the ureters, with more pronounced distention of the left ureter than of the right. The roentgenographic evidence was consistent with the existence of a recent pregnancy.

On October 25 culture of fluid aspirated from the sacral portion of the spinal canal showed that the predominating organism was a hemolytic streptococcus. Staphylococcus albus was also occasionally noted. On October 26, 2 to 3 drops of thick, purulent material was aspirated from the spinal canal at the fourth lumbar level. Prior to removal of the fluid resistance had been encountered, but whether from the ligamentum flavum or from the dura one could not be certain. The specimen, therefore, may have been from either the subdural or the epidural space. No spinal fluid was obtained during this procedure. A smear revealed numerous leukocytes and a few gram-positive diplococci. Culture yielded pure Staph. albus haemolyticus. The rest of the laboratory studies gave essentially negative results. There were slight daily elevations in temperature, to 100 or 101 F., with a corresponding rise in the pulse rate to 90 or 100 a minute. No change in the respiratory rate or the blood pressure was noted. Under routine sulfathiazole therapy, 15 grains (0.975 Gm.) every four hours for two weeks, the patient showed rapid improvement. She was asymptomatic and neurologically normal both on her discharge from the hospital, on November 10, twenty-four days post partum, and on her most recent follow-up examination, on March 11, 1944.

CASE 2.—A woman aged 22 was delivered of a normal, viable female infant, with repair of a left mediolateral episiotomy incision, on June 17, 1943. Caudal anesthesia was induced by the ureteral catheter technic, and 335 cc. of a 1.5 per cent solution of metycaine hydrochloride was given, at the rate of 20 cc. per hour. The delivery and postpartum course were uneventful, and the patient was discharged, without symptoms, on June 24. Pain in the lower part of the back with bilateral sciatic radiation, first noted on June 26, necessitated readmission on July 1. A questionable sensory level was noted at the third lumbar segment on both sides; reflexes over the lower extremities were hyperactive but equal on the two sides, and the Kernig and Brudzinski signs were present. Drainage of the urinary bladder was necessary for two weeks because of retention. The symptoms were thought to be due to epidural cellulitis, rather than to abscess. The temperature and pulse rate showed daily elevations, averaging 103 F. and 120 per minute respectively. The blood pressure and the respiratory rate presented no deviations from normal. There were accompanying leukocytosis, with a count of 10,000 white cells, and anemia, with a red cell count of 3,500,000 and a hemoglobin concentration of 75 per cent. All symptoms gradually disappeared after institution of sulfadiazine therapy, 15 grains being given every four hours for four weeks. The patient was discharged as improved on July 24.

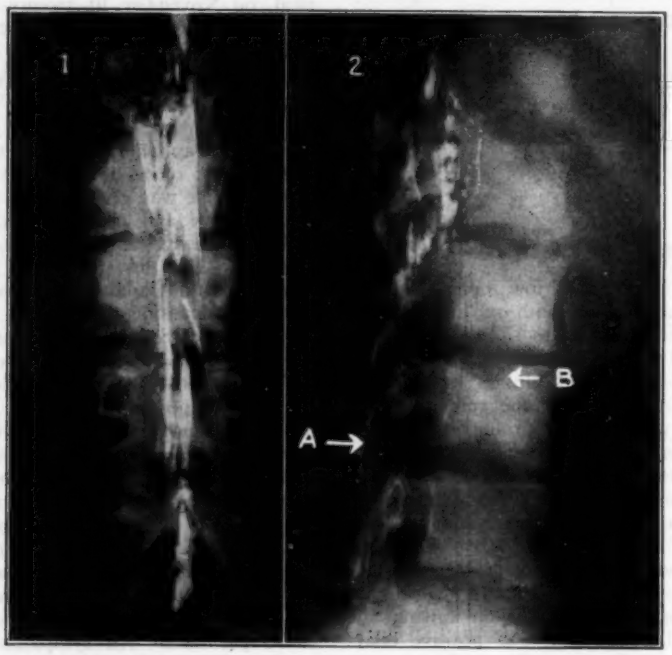
Because of continued pain and spasm over the lumbar region and the lower extremities and the development of generalized paresthesias, the patient was again admitted on August 5. There was evidence of widespread involvement of the spinal cord. The reflexes were hyperactive throughout, and the Kernig and Brudzinski signs were elicited. Slight nuchal rigidity was noted. The Babinski, Chaddock, Oppenheim and Hoffmann signs were present bilaterally, with transient patellar and ankle clonus on the left side. There was generalized muscular atrophy, which was greater in the lower extremities. The most pronounced deviations noted in a study of the blood were leukocytosis, with a white cell count of 14,800, and anemia, with a red cell count of 3,250,000 and a hemoglobin concentration of 70 per cent. The temperature, again, showed slight daily elevations to 100 or 101 F., but little change in the pulse and respiratory rates or in the blood pressure was seen. Intensive supportive therapy, including a diet of high caloric and vitamin content, administration of liver, frequent transfusions and administration of

supplementary vitamins and sulfadiazine, was instituted.

On August 11 spinal puncture at the third or fourth lumbar level yielded no fluid, but at the second lumbar level the initial pressure was 230 mm. of water. Twenty-five cubic centimeters of clear, colorless fluid was removed, and the final pressure was 130 mm. of water. No block was noted. At the fifth lumbar level the initial pressure was 130 mm. of water. The fluid was bloody, and there was evidence of partial block. A specimen of spinal fluid from the latter level contained 50 mg. of total protein and 37.5 mg. of sugar per hundred cubic centimeters and 7 lymphocytes and 11 polymorphonuclear leukocytes per cubic millimeter. No organisms were noted in smears or on culture of the fluid.

On October 15 a myelogram obtained with pantopaque[1] showed evidence of diffuse lumbar arachnoiditis (figure, *1*). Excision of the laminas from the second to the fifth lumbar vertebrae inclusive was performed on October 21. The arachnoid was firmly attached to the dura and the adjacent roots of the cauda equina. In the exposed area, the nerves were so solidly adherent that no fluid was seen, the cauda equina resembling a virtually solid column. Spinal fluid was not obtained until the level of the first lumbar vertebra was reached. A section of tantalum foil was placed over the exposed roots after they had been carefully separated, and the dura was not closed.

After operation the paresthesias and sensory changes disappeared. There was areflexia over the lower extremities, with hyperactive reflexes and a positive Hoffmann sign over the upper extremities. Retention of urine necessitated frequent catheterization, resulting ultimately in an automatic bladder. The urine during this period occasionally showed evidence of cystitis, with 20 to 30 polymorphonuclear leukocytes per high power field. Nonhemolytic staphylococci and Escherichia coli were noted in smears and on cultures. Lumbosacral pain and muscle spasm continued, however, and roentgenographic examination on December 20 showed a destructive process involving both surfaces of the bodies of the second, third and fourth lumbar vertebrae, the inferior surface of the fifth lumbar vertebra and the superior surface of the first sacral vertebra (figure, *2*). The process was most pronounced at the second and third lumbar vertebrae, with sclerosis around a cup-shaped area of dissolution in the centrum. There was slight narrowing of the second lumbar intervertebral space. Examination on Feb. 1 and Feb. 12, 1944 revealed a decreased reaction of the vertebral bodies surrounding the previously described areas of osteomyelitic destruction. Surgical treatment was not advised because of the slow, but definite, advancement, and active physical therapy was instituted. Penicillin was not given, owing to failure to obtain any organism on culture. Flexion contracture of the hip, knee and achilles tendon developed on both sides, necessitating application of casts, with frequent blocking. The patient continued to show gradual improvement, and on her last examination, on August 30, there were only slight evidence of previous contractures and moderate intermittent pain in the lower part of the back. The neurologic status was otherwise unchanged. Roentgenograms showed the presence of healing about the previous areas of involvement.



1, myelogram obtained with pantopaque, showing chronic arachnoiditis; *2*, myelogram, showing (*A*) tantalum foil, inserted at operation, and (*B*) osteomyelitic involvement of the body of the third lumbar vertebra.

The cause of the massive adhesive arachnoiditis in this case has not been determined, but it is probable that the anesthetic was introduced into the subarachnoid space. Whether the process was a sequel of the anesthesia itself and the resultant reaction, either toxic or chemical, or whether a latent organism or virus was activated or introduced at the time of injection of the anesthetic, with production of a low grade infection,

1. Pantopaque (a mixture of ethyl esters of isomeric iodophenylundecyclic acids, containing 30.5 per cent of iodine in the form of organic combinations) is a new radiopaque oil that is thinner and less viscous than the older iodized oils. It has a specific gravity of 1.263 at 20 C.

has not been determined. The presence of intermittent slight elevations in temperature was evidence of the latter. Finally, the extent of the arachnoiditis has not been determined but must be maximal in the lumbosacral region. It is hoped that separation of the roots of the cauda equina will reestablish circulation of the spinal fluid and result in ultimate recovery. The osteomyelitis might be attributed either to hematogenous spread or to direct extension.

COMMENT

Hingson and Edwards [2] recently analyzed critically the collected results in the first 10,000 cases in which continuous caudal anesthesia was used. They reviewed the entire subject, but we are concerned only with the neurologic sequelae, the incidence of which constitutes 2.2 per cent of all complications recorded.

Occasional need for catheterization is not uncommon, and only 1 case was mentioned in which there was urinary retention of three weeks' duration. The authors state the opinion that injection of metycaine in distilled water may produce neuritis as a result of contact of the nerve trunks with the products of hemolysis of the red cells. Use of the lateral recumbent position prior to delivery has largely obviated the early high incidence of pain in the lower part of the back. The convulsions present in 2 of the authors' cases were due to accidental intravascular injection and an overdosage of the anesthetic. Both patients recovered. Headaches were transient and were attributed to too rapid a rate of injection. In 2 cases there was subjective numbness—in 1 case with a level at the fifth cervical segment, which cleared in three weeks, and in the other with sensory impairment in the vaginal vault and the perineum, which had continued until the time of the report, for three months. In 1 case a transient hysterical reaction developed during anesthesia. Vertigo, tinnitus and visual changes were also mentioned.

The incidence of severe cellulitis or peridural abscess was 0.05 per cent. A staphylococcic infection of the extradural space at the fifth lumbar and the first sacral levels, with bacteremia, was responsible for death, thirty-one days post partum, in 1 case. In the remaining cases the patients responded to treatment with sulfonamide compounds. In the routine therapy of this complication the authors suggested aspiration of purulent exudate from the caudal part of the canal and instillation of 75,000 units of penicillin in 40 cc. of isotonic solution of sodium chloride, to be repeated at least once two hours later. If incision and drainage are necessary, irrigation with a 5 per cent solution of sulfathiazole is recommended every hour for twelve hours. The oral use of the sulfonamide compounds is maintained when the patient is resistant to penicillin and when the latter drug is not available.

An additional complication recorded by Manalan [3] is the development of staphylococcic meningitis on the third postpartum day. This sequela was attributed to the employment of caudal anesthesia, although aspiration of the contents of the sacral portion of the canal gave no evidence of infection. Recovery was complete. Bishop [4] mentioned drowsiness, vomiting, pyrexia, a rise in the level of anesthesia and paresis of the right side of the face and the right arm after the use of metycaine. Subdural injection probably resulted, and the patient's weakness gradually disappeared after her discharge from the hospital.

SUMMARY

We have presented 2 obstetric cases with unusual complications following the use of continuous caudal anesthesia. In 1 case the sequela was either an epidural or a subdural abscess, which responded to treatment with a sulfonamide compound with complete recovery. The exact location of the abscess was not determined, as no operation was performed. This case was previously briefly reported by Siever and Mousel [5] as that of epidural abscess. The other complication was arachnoiditis involving the cauda equina with secondary osteomyelitis, the final outcome of which is still in doubt because of a residual pathologic process. It appears, therefore, that the role of infection in the production of complications following the use of caudal anesthesia is second only to the introduction of the anesthetic into the subarachoid space, and this view has also been recently expressed by Gready.[6]

2. Hingson, R. A., and Edwards, W. B.: Continuous Caudal Anesthesia, J. A. M. A. **123**:538 (Oct. 30) 1943.

3. Manalan, S. A.: Caudal Block Anesthesia in Obstetrics, J. Indiana M. A. **35**:564 (Oct.) 1942.

4. Bishop, H. F.: Continuous Caudal Anesthesia, S. Clin. North America **23**:1565 (Dec.) 1943.

5. Siever, J. M., and Mousel, L. H.: Continuous Caudal Anesthesia in Three Hundred Unselected Obstetric Cases, J. A. M. A. **122**:424 (June 12) 1943.

6. Gready, T. G.: Some Complications of Caudal Anesthesia and Their Management, J. A. M. A. **123**: 671 (Nov. 13) 1943.

Case Reports

MENINGIOMA OF THE VELUM INTERPOSITUM

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Cushing divided meningiomas of the tela choroidea superior (velum interpositum) into two groups, lateral and posterior tumors of the velum. Posterior tumors of the velum are indeed rare. In a review of the literature reports of but 4 such tumors were found. Horrax,[1] in 1936, resected the occipital lobe and removed successfully a meningioma, weighing 40 Gm., overlying the quadrigeminal region. The tumor was of fibroblastic type, with no psammoma bodies. Araki[2] had experience with 2 meningiomas in this location. Both tumors were successfully attacked by splitting the splenium of the corpus callosum and removing the growth piecemeal. One of these tumors had psammoma bodies and was visible roentgenographically. The tumor reported by Balado and Tiscornia[3] was a meningioma arising from the free posterior margin of the falx cerebri. Suboccipital exploration in two stages for an associated medulloblastoma in the midline of the vermis terminated fatally.

The following case is that of a psammomatous meningioma of the posterior portion of the velum interpositum. The tumor was approached by a combined suboccipital and occipital craniectomy, with section of the tentorium.

REPORT OF A CASE

History.—Miss C. H., aged 13, was admitted to Dr. S. F. Gilpin's neurologic service at Temple University Hospital on Jan. 3, 1944, having been referred by Dr. Alexander Silverstein, of Philadelphia.

Except for a reported attack of rheumatic fever four years before, she had apparently been well until six months prior to admission, when headaches appeared in the right temporal region. The attacks lasted approximately two hours and could be relieved by medication. A history of definite disturbance in gait could not be obtained, but the mother stated that walking had always been somewhat irregular. The left pupil had been larger than the right since birth. One week before admission the patient noted sudden onset of numbness of the left side of the face, which progressed downward to involve the whole left side of the body. The entire episode was of fifteen minutes' duration. At this time a physician noted increase in headache, vomiting, somnolence, inability to concentrate and unsteadiness of gait. During the week prior to hospitalization there were frequent attacks of fainting, with respiratory distress. She was accordingly referred to the neurologic service for observation.

Examination.—The patient was well nourished and cooperative. General physical examination revealed nothing significant. Neurologic examination revealed the following signs: There was a "cracked pot" sound on percussion of the skull, indicating increased intracranial pressure. The gait showed mild ataxia, with swaying to the left side. Both pupils were dilated, but the left one was larger than the right. The pupils did not respond to light but reacted to accommodation. The fundi revealed bilateral papilledema of 2 D. A relative central scotoma was present in the left eye. The extraocular movements appeared full in all directions except for partial weakness of upward gaze. On the patient's looking downward, there was a rotatory nystagmus in the clockwise direction. On her looking to the right, there was horizontal nystagmus to the right with a clockwise rotatory component. On her looking to the left, there was left horizontal nystagmus with a rotatory clockwise component. The corneal reflexes were active and equal on the two sides. No sensory or motor disturbances were noted in any of the trigeminal fields. The expressional movements of the face were normal. Audiometric readings showed partial conduction deafness in the right ear. There was no hoarseness or dysphagia. The ninth, tenth, eleventh and twelfth cranial nerves did not appear to be involved.

The deep tendon reflexes were notably decreased, but the Babinski sign could easily be elicted bilaterally. The Hoffmann sign could not be obtained. Sensory disturbances were not noted in any of the cutaneous dermatomes.

There was striking generalized hypotonia, with mild dysmetria and adiadokokinesia, on the left side. Tension of the muscles of the neck was increased, however. When the arms were raised above the head, the left forearm flexed at the elbow, and the hand deviated laterad. The entire left extremity deviated away from the midline.

The laboratory studies, including serologic tests, gave normal results.

Roentgenograms of the skull showed a dense calcification, about the size of a pigeon egg, in the midline, just inferior to the usual position of the pineal body (fig. 1). There were other signs of increased intracranial pressure, such as widening of the suture lines, erosion of the dorsum sellae and a silver-beaten appearance of the inner table of the skull.

The patient was transferred to Dr. M. Scott's neurosurgical service for operation.

Operation (January 2).—Suboccipital craniectomy combined with occipital craniectomy and tentorial section was carried out.

The patient was placed in the cerebellar position. A flap was constructed on the right side, the vertical limit of which extended from the spinous process of the

From the Neurosurgical Service, Temple University Hospital and School of Medicine.

1. Horrax, G., cited by Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C Thomas, Publisher, 1938.

2. Araki, C.: Meningioma in the Pineal Region: A Report of Two Cases Removed by Operation, Arch. f. jap. Chir. **14**:1181-1192, 1937.

3. Balado, M., and Tiscornia, A.: Tumor de la hoz del cerebro pediculado a desarrollo subtentorial, Arch. argent. de neurol. **1**:297-310, 1927.

second cervical vertebra to a point 6 cm. above the external occipital protuberance. From this point the incision was carried in a semicircular fashion down behind the right ear to the tip of the mastoid. The ventricle was tapped immediately, and clear fluid was released slowly, under tremendous pressure. An indwelling cannula was inserted into the ventricle and allowed to remain in place during the entire procedure.

The musculoaponeurotic flap was then dissected from the bone overlying the cerebellum and the occipital lobe. The laminas of the atlas and axis were exposed, and the lamina of the atlas was removed. The bone was then rongeured away over the right side of the cerebellum and over the right occipital lobe up to and including the burr opening into the ventricle. The bone was also removed over the left cerebellar hemisphere.

The dura was opened with a fishhook incision over the cerebellum and the flap turned downward. The dura was opened over the occipital lobe, with the base of the flap parallel to the transverse sinus. Large veins passing from the occipital lobe to the transverse sinus were carefully cauterized and divided. The occipital lobe was displaced upward and laterad and the tentorium sectioned, so that the following structures were revealed: (1) the transverse sinus, (2) the superior longitudinal sinus, (3) the inferior longitudinal sinus, (4) the straight sinus and (5) both internal cerebral veins (veins of Galen).

The tumor could then be seen in the depths of the wound, just below the region of the pineal gland, the upper pole projecting beneath the pineal gland and obstructing the aqueduct. The tumor was whitish and the size of a flattened hen's egg, surrounded by dense adhesions and numerous tortuous vascular channels. A hypodermic needle was inserted into the tumor, and about 1 cc. of yellowish, cystic contents was evacuated. After tedious and prolonged dissection, it was concluded that approximately three fourths of the tumor had been removed. Although the patient's condition was excellent, it was decided to remove the remaining portion at a second stage, in view of the long operative siege.

The tentorium was not sutured. The dura over the cerebellum and the occipital lobe was closed loosely with interrupted silk sutures. A drain was placed in the epidural space above the level of the foramen magnum. The subcutaneous layers and the skin were closed with interrupted silk sutures. The immediate postoperative condition was excellent.

Postoperative Course.—First Day: During the night the temperature and the pulse and respiratory rates increased, and the systolic blood pressure rose slightly. On the following morning respiration became rapid and labored. The spinal fluid pressure was 30 mm. of mercury, and the fluid was blood tinged; 30 cc. was slowly removed. Respiration immediately improved, and the systolic blood pressure was lowered.

The right lateral ventricle was tapped, and the fluid was noted to be under great increase in pressure. Approximately 100 cc. of fluid was slowly removed. Two hours later breathing again became labored and rapid, and there was a crowing type of respiration, with indrawing of the suprasternal structures. Emergency laryngoscopy was performed, and a large, silk-woven catheter was inserted through the edematous vocal cords. Breathing immediately improved and became quiet. Two hours later the pulse became rapid; the face and neck were edematous; the face was flushed; the temperature was 104 F. (rectal), and the dressing was profusely wet. The dressing was reinspected, and a cotton wick was placed in the opening of the cannula. Meanwhile the patient was given 500 cc. of plasma and 500 cc. of whole blood. The chemical constituents of the blood were then normal, and the patient's condition was distinctly improved. The respiratory rate was still 36 to 40 per minute, but breathing was easier and without obstruction. Carbon dioxide and oxygen were given almost continuously.

Second Day: The patient's condition was somewhat improved. Respiration was still labored. There was slight movement to painful stimuli and definite movement when spinal drainage was carried out. The initial spinal fluid pressure was 22 mm. of mercury, and 40 cc. of clear, xanthochromic fluid was slowly removed. The respiratory rate immediately increased somewhat, and there was definite movement of all the limbs. The

Fig. 1.—Roentgenograms of the skull, showing the size and position of the calcified tumor.

right pupil was dilated, and the left pupil was unchanged. There was no response to light. The dressing was wet with the fluid from the draining intraventricular cannula.

Fifth Day: Respiration was so labored and obstructed that bronchoscopic aspiration had to be done on several occasions to clear the upper tracheal passages of crusts and mucopurulent exudate. A tracheotomy was performed by Dr. Charles Norris, with immediate improvement in the patient's condition.

Next Nine Days: The patient had recurrences of respiratory difficulty, with periods of apnea and Cheyne-Stokes respiration. Several times respiration ceased and had to be restored by artificial means. At these times the operative flap became full and bulging, and ventricular puncture offered only temporary relief. At other times the tracheotomy tube became filled with crusts, requiring changing of the tube, and even repeated bedside bronchoscopic aspirations which were done by Dr. Charles Norris.

Sterile methylrosaniline chloride, introduced into the ventricular system, could not be recovered from the spinal fluid below the level of injection. This indicated a block, probably in the region of the aqueduct of Sylvius.

January 21: Jacksonian seizures were seen to involve the arm, face and leg on the right side. That evening, because of increased respiratory difficulty, a second exploration was decided on. Dr. Michael Scott suggested that the Torkildsen procedure might be used with benefit.

Reexploration.—The former craniotomy flap was elevated. The right cerebellar hemisphere was noted to be twice its size, swollen and tense, and the tonsil on the right side had herniated through the lower dural opening. The foramen magnum on the patient's left side was further decompressed. The dural constriction was cut. It was almost impossible to view the former operative site.

After intravenous administration of 20 cc. of 20 per cent sodium chloride, edema subsided and more room was available. The tonsils of the cerebellum were separated, and a ureteral catheter was inserted along the floor of the fourth ventricle, through the aqueduct of Sylvius and into the third ventricle. The course of the catheter was verified by passing air into the catheter below and observing its escape from the cannula in the ventricle above, which indicated a release of the block.

A second, no. 14 French, catheter, was inserted into the lateral ventricle in place of the cannula and passed around the cerebellum to the foramen magnum below; thus a ventriculostomy was done. The dura was allowed to remain open. The fascial layers were closed with silk as usual; the skin was closed with silk, and only the ureteral catheter was drawn out through the incision.

The most gratifying result was the immediate abeyance of the Cheyne-Stokes respiration. Breathing, although rapid, was regular. The color was good, and the condition was improved.

Postoperative Course.—On the two following days Cheyne-Stokes respiration did not recur, but breathing became more rapid and shallow. The spinal fluid pressure was 10 mm. of mercury, but there was still xanthochromia. The tracheotomy tube functioned satisfactorily. Both pupils were dilated, with no response to light. The corneal reflex was not obtained. The left eyeball was turned downward and outward.

Nineteen days after the original operation, or nine days after the second exploration, a sudden hemorrhage occurred from the tracheotomy tube, resulting in sudden asphyxia and death.

A roentgenogram of the skull was taken post mortem to verify the position of the catheters, as well as to ascertain the amount of the tumor removed (fig. 2). No evidence of the calcification seen in the tumor on the original films could be found. The ureteral catheter was observed to pass from the fourth ventricle through the aqueduct of Sylvius into the third ventricle. The large catheter from the right lateral ventricle to the foramen magnum (ventriculostomy) was in its proper position.

Histologic Character of Tumor.—The pathologic specimen measured 4 cm. in its greatest diameter. The meningeal surface was glistening but notably injected. The underlying portion had a grayish white, granular appearance, and palpation imparted a gritty sensation. Microscopic examination revealed a loose, vascular, edematous stroma, interspersed with numerous ovoid spindle cells. At times the spindle cells displayed a tendency to arrange themselves in bundles. Scattered profusely throughout the tumor were numerous psammoma bodies. The diagnosis was meningioma.

Postmortem Examination.—There was pronounced internal hydrocephalus. No evidence of residual tumor tissue was to be seen. Inspection of all the great venous sinuses, including the vena cerebri magna and the internal cerebral veins, failed to show any evidence of thrombosis. The ureteral and the no. 14 French rubber catheter were noted to be in the positions shown in the roentgenogram.

Fig. 2.—Roentgenogram of the skull, taken post mortem, showing passage of the ureteral catheter along the floor of the fourth ventricle through the aqueduct of Sylvius. A partial ventriculogram was obtained by injection of air into the ureteral catheter at its exit. The larger rubber catheter is seen to pass from the lateral ventricle around the cerebellum, beneath the skin, to the foramen magnum area below. Note the absence of the calcified tumor shown in figure 1. The centrally placed clips mark the position of removal of the tumor.

COMMENT

A possible successful surgical result was terminated by a fatal hemorrhage from the tracheotomy wound. Retrograde catheterization of the aqueduct of Sylvius is a feasible, and not especially difficult, procedure. This may be employed

in other cases of aqueductal obstruction. The Torkildsen procedure of ventriculostomy may likewise be tried. Torkildsen [4] reported some degree of success in 3 cases. Penfield [5] reported successful use of the method in a case of inoperable obstruction of the aqueduct.

The operative procedure of tentorial section in cases of tumors of the pineal region has been practiced and developed by Fay.[6] The approach gives sufficient accessibility to the tumor area and offers promise of successful surgical outcome in these hopeless cases. If the tumor should prove inoperable, roentgen therapy may be employed to better advantage, with division of the constricting ring of the tentorium.

It was interesting to note that no trace of tumor was evident post mortem. The position of the tumor indicated a probable origin from the posterior part of the velum interpositum. The tumor lay at the junction of the inferior longitudinal sinus, the straight sinus and the vena cerebri magna. The growth probably compressed the veins in this region, but whether the venous compression was the cause of the internal hydrocephalus is a matter of conjecture. The most probable cause was the obstruction of the aqueduct of Sylvius. The position of the tumor was similar to that reported by Balado and Tiscornia.[3]

Temple University Hospital.

4. Torkildsen, A.: New Palliative Operation in Cases of Inoperable Occlusion of Sylvian Aqueduct, Acta chir. Scandinav. **82**:117-123, 1939; abstracted, Acta psychiat. et neurol. **14**:221, 1939.

5. Penfield, W.: Torkildsen Procedure for Inoperable Occlusion of the Sylvian Aqueduct, Canad. M. A. J. **47**:62-63, 1942.

6. Fay, T.: The Management of Tumors of the Posterior Fossa by the Transtentorial Approach, S. Clin. North America **10**:1427-1459, 1930.

Clinical, Technical and Occasional Notes

SPONTANEOUS IMITATIVE MOVEMENTS

Report of a Case

MAJOR H. H. GOLDSTEIN AND CAPTAIN RAYMOND SOBEL
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REPORT OF CASE

A white man aged 19 was admitted to the neuropsychiatric service of a station hospital on Feb. 20, 1943. The patient, who was right handed gave as his chief complaint a mimicking disturbance of movement in the hand opposite the one used in carrying out voluntary action. The disorder had been present from birth. A farmer and ship's fitter, he occasionally went on alcoholic sprees, but drank less than a pint (500 cc.) once or twice a month. He smoked one package of cigarets daily.

Family History.—There was no history of familial or hereditary disease. His mother and one sister were left handed, and two other sisters were twins.

Personal History.—The patient had an attack of appendicitis six months prior to admission. He had had chills and fever, of unknown origin (not malarial), at the age of 15 years. At 12 years of age he was told by his physician that he had high blood pressure but that there was no evidence of nephritis. No symptoms referable to the gastrointestinal, urinary, respiratory and cardiovascular systems were present. There had been no injuries.

Present Illness.—Involuntary, simultaneous, "imitative" motion of the hand, and occasionally of the arm, on movement of the other hand or arm was first noticed by his parents when he was 4 or 5 months old. This symptom had persisted, with only slight improvement. The "imitative" movement mimicked the movement of the opposite hand or arm, but was less extensive; as a result he had always been somewhat clumsy in maneuvers which require dissociated motions of the arms, such as those used when a hammer is held in the right hand to hit a nail in the left hand (the patient's left hand swung in unison, but in miniature, with the right hand, so that he missed). Rarely, on his raising one arm, the other tended to follow. He had never noticed this phenomenon in his legs or feet but stated that he had always been somewhat slow in walking or running. It had not prevented him from working as a ship's fitter. Although it took him longer to perform tasks requiring dissociated dexterity of the hands, he circumvented the difficulty by fixation of one hand, so that it would be forced to remain in place. He was a good dancer and liked to "jitterbug." He had always been aware of weakness in his left arm and hand and stated that he could not "feel things" as well with the left hand and foot; by this he meant a stereognostic defect. As a result, he had used his right side practically to the exclusion of the left. To his knowledge, all the members of his immediate and distant family had normal coordination.

He had never noticed any disturbance of taste or smell or any diplopia, teichopsia, amblyopia or amaurosis. Tinnitus, as a result of his working near riveters, had been present on occasion. He had had no abnormality or disturbance of sensation. The occurrence of convulsions, loss of consciousness and epilepsy was denied, as was the presence of shooting pains, girdle sensations, unsteadiness of gait or falling in the dark. Bowel and bladder sphincter control had always been intact, and sexual function was normal.

Although the patient had noticed improvement in dexterity during the past three years, he attributed it to practice in voluntary dampening and inhibiting of the contralateral movement. There had been no true remission or relapse. Aside from the weakness and asynergy of his left arm, no other symptoms were noted.

Neurologic Examination.—Cranial Nerves: First pair: Olfactory function was intact.

Second pair: The disks were normal, with no papilledema or optic nerve atrophy.

Third, fourth and sixth pairs: Extraocular movements were normal. The pupils were equal and active and reacted well to light and in accommodation. Slight hippus was noted in reaction to light. There was no nystagmus, paresis or paralysis. Ability to blink either eye singly was not tested.

Fifth pair: The trigeminal nerve was intact and normal. The corneal reflexes were active.

Seventh pair: The facial nerve was intact and normal.

Eighth pair: Bone conduction was less than air conduction. Sounds were not lateralized. Response to the Weber and Rinne tests were normal.

Ninth nerve: The gag reflex was present.

Tenth pair: There was no deviation of the palate.

Eleventh pair: Power in the sternocleidomastoid and trapezius muscles was normal and equal on the two sides.

Twelfth pair: The tongue protruded in the midline.

Motor Nerves: There was slight diminution of power in the upper and lower extremities on the left side, the loss involving all motions but being most noticeable in the distal portions and in the finer motions of the phalanges, wrist, toes and forefoot. Power in the muscles with cranial innervation was intact. The right side of the body was normal.

Tonus: There was slight but definite hypotonicity of the upper and lower extremity on the left side, with minimal spooning of the left hand. Rebound was more pronounced on the left side than on the right.

Coordination: Gait was normal. Turning to the right was poorly accomplished, whereas turning to the left presented no difficulty. There was slight swaying to the left in the Romberg test. Coordination was normal on the right side, but slight ataxia and intention tremor of the left arm were present in the finger to nose test. Asynergy and ataxia of small movements of the left hand were elicited on repetitive movements. There was no drift on extension of the arms.

Reflexes: All the deep reflexes were present in normal degree on the right side and were slightly increased throughout on the left side. Abdominal reflexes were present but were easily exhausted on both sides. There were equivocal fanning and dorsiflexion of the large toe on plantar stimulation, and frequently spontaneous bilateral and unequivocal extensor plantar signs appeared in tests of motor function of the lower extremities. The Chaddock, Oppenheim and Hoffmann signs were absent. A blow on the ball of the foot produced flexion of the toes on the left side only (Rossolimo sign).

Sensory Status: Pain, touch, temperature and vibration senses were intact throughout.

Stereognosis: The patient recognized the depth and shape of coins with the right and the left hand, but poorly with the left. He failed to distinguish the configuration of a paper clip with the left hand. He pointed out arcs of a circle well with both arms but distinguished them poorly with the fingers of the left hand.

Two point discrimination: Epicritic sensibility was diminished on the left side. Two points separated 1 cm. were identified as one over the pads of the fingers of the left hand, whereas discrimination of points separated as much as 3 mm. was present in the right hand. Discrimination sense was diminished over the entire left half of the body.

Associated Movement: There was no adiadokokinesis in gross motions at the wrist or at the metacarpophalangeal joints. However, repetitive movements of the phalanges on the left side were impaired, asynergic and ataxic.

The disturbance of motion was illustrated by the following test: On flexion of the first and second phalanges of the fingers of the right hand there was involuntary, simultaneous and "imitative" flexion of the first and second phalanges of the left hand. This movement occurred in miniature, the phalanges on the left side moving only 1 cm. or so. This "imitative" movement was present to a lesser degree when the voluntary movement was carried out with the left hand. Flexion, extension or rotation at either wrist produced contralateral movement of like nature, but of lesser degree, in the opposite extremity, the "imitative" movement being more pronounced in the left extremity. The more proximal the movement, the less apparent was the phenomenon; this was also true of axial movements. The patient stated that he had been able to inhibit the involuntary axial motions at the shoulder by practice, and hence they were observed only when he felt that he was not being watched. Although he had never noticed the "imitative" movement in his lower extremities, it was as apparent in the toes as in the hands. However, movement of the toes of the left foot did not produce movement of the toes of the right foot, as in the case of the arms. This was also true of the seldom observed "imitative" motion of the axial joints. There was dissociation of movement in the phalanges of the left foot which was not present in those of the right foot; with grasping motions of the small toes of the left foot, the large toe went into dorsiflexion, whereas on the right side the toe was plantar flexed with the remaining digits.

The greater the patient's awareness of the motions carried out, the less evident was the "imitative" motion. Old, habitual patterns, such as writing and buttoning the shirt, were more productive of contralateral motion. No contralateral movement was attained in involuntary motion stimulated reflexly; that is, production of a knee jerk on the right side did not produce a contralateral knee jerk. The Magnus and De Kleijn reflex and crossed extensor reflexes were not elicited, and there was no evidence of decerebrate activity.

Aphasia: There was no anomia, alexia, agraphia or acalculia, either expressive or receptive. The patient was right handed and had no directional confusion. He followed seriatim commands and performed seriatim mental calculations. No semantic disturbances were evident. He had had difficulty in pronouncing his second name, Edmund, in grade school, but this did not persist.

Psychiatric Status.—There was no evidence of any psychiatric disorder. No hysterical phenomena were noted.

Systemic Examination.—The only relevant physical signs were a rough protruberance, about 2 by 2 cm., in the right occipital region, which underlay a sebaceous cyst, and enlarged inguinal lymph nodes secondary to epidermophytosis.

The blood pressure was 118 systolic and 76 diastolic. The temperature, pulse and respiration were normal. The blood count revealed 4,780,000 red cells, with 85 per cent hemoglobin, 6,850 white cells and a normal differential count. Urinalysis revealed that the specific gravity and the microscopic constituents were normal, and the reactions for sugar and for albumin were negative. The sugar, cholesterol and nonprotein nitrogen contents of the blood were within normal limits.

Roentgenographic examination of the skull revealed nothing abnormal. Spinal puncture showed normal pressure and normal dynamics. The fluid was clear. The Wassermann reaction of the fluid was negative; the colloidal gold curve was 000000000; the sugar level was normal; the protein measured 35 mg. per hundred cubic centimeters, and the cell count revealed 2 lymphocytes per cubic millimeter.

SUMMARY

An apparently congenital, unremitting disease of the central nervous system in a 19 year old white man was manifested by inability to dissociate motor function of one side from that of the contralateral side. Spontaneous, simultaneous, involuntary and seemingly imitative motion of a lesser degree occurred in the part contralateral to that voluntarily moved. Mild hemiparesis, incoordination, cortical sensory signs and slight reflex changes were demonstrable in the left extremities.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE EFFECT OF ERGOTAMINE TARTRATE AND NEOSYNEPHRIN HYDROCHLORIDE ON THE WORK CAPACITY OF HUMAN MUSCLE. GEORGE C. KOTALIK, GEORGE L. MAISON and CARL PFEIFFER, Am. J. M. Sc. **206**:503 (Oct.) 1943.

The authors proposed to determine, if possible, whether therapeutic doses of ergotamine tartrate would consistently produce muscle weakness in normal persons. The Maison ergograph was used to the point of fatigue to measure the work capacity. Ten thoroughly trained subjects were used after a training period varying from three to fourteen months, during which time the muscles of each arm were worked to fatigue six days a week. The work ability was tested at the height of the action of the drug ninety minutes after the intramuscular injection of 0.25 to 0.75 mg. of ergotamine tartrate, or fifteen to thirty minutes after the intramuscular injection of 4 to 10 mg. of neo-synephrin hydrochloride. In general, no significant decrease in work output occurred after the intramuscular injection of ergotamine tartrate. Subjective symptoms due to ergotamine tartrate were surprisingly few, even with doses of 0.75 mg. The most significant observation was the increase in work capacity after the intramuscular injection of neo-synephrin hydrochloride. The authors conclude that the muscle weakness occasionally reported from the use of ergotamine tartrate in cases of migraine headache cannot be due entirely to the drug.

MICHAELS, Medical Corps,
Army of the United States.

EFFECT OF PHYTONCIDES UPON PROTOZOA. B. TOKIN, Am. Rev. Soviet Med. **1**:237 (Feb.) 1944.

Phytoncide is the name applied to the volatile substances produced by plants in their life cycle and endowed with strong bactericidal and protistocidal properties.

Tokin states that "small amounts of a paste of freshly macerated onion, garlic or other plant emit enough phytoncides to kill all exposed unicellular organisms within 1-5 minutes." The species of protozoa most thoroughly investigated was Paramecium caudatum. Phytoncide was found to be common in many plants investigated, and the author states that apparently "the effect of phytoncides upon bacteria, fungi, or protozoa is biochemical in nature." Such factors as the plant source of the phytoncide, the distance (1-1.5 cm.) between the phytoncide and the test object and the rate of dissipation of the vapor modify the results of the experiments.

GUTTMAN, Philadelphia.

ACTION OF PHYTONCIDES UPON INFUSORIA. A. KOVALENOK, Am. Rev. Soviet Med. **1**:239 (Feb.) 1944.

Kovalenok reports that phytoncides produced a lethal effect on several species of free-living infusoria, on some flagellates and on a parasitic infusorium found in the pig intestine. A phytoncide from one plant applied for equal lengths of time to various species of infusoria varied in the mechanism of their action. The species of protozoa was the determining factor. The effect, however, was always lethal for the protozoa.

The author concludes that the experiments on protozoa may be helpful in investigating the action of phytoncides on cells and tissues of multicellular organisms. The results may suggest a practical application of phytoncide therapy to the control of pathogenic protozoa.

GUTTMAN, Philadelphia.

EFFECT OF PHYTONCIDES ON RABBITS. I. TOROPTSEV, Am. Rev. Soviet Med. **1**:242 (Feb.) 1944.

Toroptsev subjected healthy rabbits, 6 to 10 months old, to vapor from freshly prepared onion paste. The treatment was given for four minutes, ten times a day, for ten consecutive days. Fresh onion paste was employed for each treatment. The animals were killed at various times—one, five and fifteen days after the last inhalation.

There were an inflammatory reaction of the respiratory organs and stimulation of the reticuloendothelial system, the cells of which were phytonotropic in rabbits which were killed one and five days respectively after the termination of the inhalations. In the rabbits killed fifteen days after termination of exposure to the phytoncide the only abnormality was persistence of swelling of the Kupffer cells. From this the author concludes that the liver probably served as a barrier, since it still exuded an odor of onions.

The author concludes that the inhalations of phytoncides in high concentrations produced slight, and entirely reversible, changes in the tracheobronchial tree, the liver and the kidney of the rabbit.

GUTTMAN, Philadelphia.

THE EFFERENT PATHWAY FOR PUPILLARY CONTRACTION. P. W. NATHAN and J. W. ALDREN TURNER, Brain **65**:343, 1942.

Nathan and Turner present evidence that two separate pathways for efferent pupilloconstrictor fibers must exist. The usually accepted pathway for pupilloconstrictor fibers is that in which the fibers run from the nucleus of the third nerve with the oculomotor nerve to the inferior oblique muscle and branch off to the ciliary ganglion. Distal to this ganglion they form several short ciliary nerves, which run through the sclera, forming the ciliary plexus, which innervates the sphincter muscle of the iris. If this were the only pathway available, its interruption should result in failure of the pupil to react either to light or in convergence. The authors, however, cite the experiments of Foerster, Gagel and Mahoney in which pupillary contraction in convergence persisted after removal of the ciliary ganglion. This observation, the authors believe, indicates that the accepted pathway subserves only the light reflex and that another pathway exists for the reflex constriction of convergence. In addition, Nathan and Turner report 10 clinical cases from the literature and 2 cases from their personal observations which demonstrate a differential paralysis of the pupillary constriction to light. The criteria established to prove that the lesion

is in efferent, rather than in the afferent, path are as follows: The pupil on the normal side must contract when the affected eye is illuminated; (2) the affected pupil must not constrict to light or dilate in darkness, either directly or consensually; (3) both pupils must contract normally in accommodation and convergence and dilate afterward, and (4) the lesion must be known to be peripheral.

The 2 personally observed cases are reported in detail: In 1 case a penetrating shell fragment came to rest on the floor of the middle fossa, just over the foramen ovale, and in the other a fracture occurred, with compression of the sphenoid fissure. Both cases fulfilled the aforestated criteria. From this evidence the authors conclude that the Argyll Robertson pupil may be due to injury of the efferent pathway to the pupil and that two efferent pathways for pupillary contraction, one subserving the light reflex and the other accommodation-convergence synkinesia, must exist. Four possible routes which the efferent fibers, which conduct the impulse to contract in accommodation and convergence, may take are considered: (1) with the sympathetic fibers, (2) via the extraocular muscles, (3) via the optic nerve, and (4) via the nasociliary nerve. The authors present evidence eliminating each of the aforementioned paths as a possibility. Finally, they offer the hypothesis that these fibers run from the third nucleus to the episcleral ciliary ganglia, thence relaying to the ciliary body, without passing through the ciliary ganglion.

SHENKIN, Philadelphia.

Psychiatry and Psychopathology

THE SPIROGRAM IN CERTAIN PSYCHIATRIC DISORDERS. JACOB E. FINESINGER, Am. J. Psychiat. **100**:159 (Sept.) 1943.

Finesinger describes a method of scoring irregularities in the spirographic record. To arrive at a simple numerical score the method employs seven variables: sighing respirations, major and minor fluctuations of the upper and lower lines of reference and point off the upper and lower lines. Tracings were obtained from 100 psychoneurotic patients, 60 schizophrenic patients and 103 normal controls.

The highest mean score was obtained for patients with anxiety, and the lowest mean score, for patients with schizophrenia and for normal subjects. The mean values for patients with hysteria and for patients with reactive depressions fell between these two extremes. The differences in the scores for patients with anxiety and the scores for patients with schizophrenia and for normal subjects were statistically valid. Sighing respirations and major fluctuations were most frequent for patients with anxiety and least frequent for normal subjects. These differences were statistically significant. The only statistically significant difference between the scores for schizophrenic patients and the scores for normal control subjects was found in the lower frequency of fluctuations from the upper line among schizophrenic patients.

FORSTER, Philadelphia.

ORGANIZATION OF PSYCHIATRIC SERVICES IN BATTLE AREAS. N. N. TIMOFEEV, Am. Rev. Soviet Med. **1**:264 (Feb.) 1944.

Timofeev stresses the necessity of mobile psychiatric units for use in theaters of operation. The special field psychiatric unit has five main functions: (1) to classify psychiatric casualties which come from the front; (2) to treat men who can be helped within four to six weeks; (3) to prevent evacuation of mildly neurotic patients, (4) to provide psychiatric consultation to medical installation and rehabilitation centers, and (5) to provide consultation to field hospitals with small psychiatric wards.

Psychiatric patients should be grouped in special hospitals as near the front as possible. Group therapy and the psychiatrist's understanding help to restore self respect and morale.

GUTTMAN, Philadelphia.

REHABILITATION OF THE WAR WOUNDED IN THE SOVIET UNION. A. N. SUKHOV, Am. Rev. Soviet Med. **1**: 293 (April) 1944.

Soviet law divides veterans into three classifications for pension purposes: (1) totally handicapped persons needing hospitalization; (2) totally handicapped persons not needing hospitalization, and (3) veterans now unfit for their previous occupations but capable of less exacting work. The amount of pension depends also on military rank and the veteran's former wages. A war invalid continues to receive a pension, in addition to his wages, when he returns to work.

Rehabilitation facilities and pensions are administered by the People's Commissariat of Social Security of the U. S. S. R. Facilities include research institutes, laboratories, polyclinics, schools, rest homes, sanatoriums and cooperative societies. War invalids attend free training schools and receive pay during the period of training. Individual consideration is given to the veteran's course of retraining, as well as to his job assignment. By August 1943, 91 per cent of the partially disabled veterans in the Soviet Union were employed.

Retraining units are incorporated into many hospitals and cover a wide variety of industrial and agricultural occupations. These units supplement the veterans' vocational schools and boarding schools, which are under medical supervision.

Prostheses are manufactured and fitted by the state. Sukhov states that a patient who uses a prosthesis is usually able to work in from two to four months after the amputation. Particular attention is given to men who have lost both arms or both legs, including the fitting of special prosthetic devices and occupational training.

Wounded veterans receive certain privileges, including an annual vacation and full sickness benefit. They also have some tax exemptions and priorities on consumer goods. Mutual aid societies contribute further forms of assistance to veterans.

GUTTMAN, Philadelphia.

HYPERTENSION IN ONLY ONE OF IDENTICAL TWINS. MEYER FRIEDMAN and J. S. KASANIN, Arch. Int. Med. **72**:767 (Dec.) 1943.

Friedman and Kasanin report a case of hypertension in one of identical twins. Studies included routine physical examination, psychologic assay, electrocardiographic study and determination of the renal blood flow and the glomerular filtration rate for each twin.

Renal function tests revealed that the blood flow in the kidneys was similarly reduced in the normatensive and in the hypertensive twin and that the glomerular filtration rates were also similar. Electrocardiograms for the hypertensive twin revealed definite evidence of myocardial damage, while the tracing made for his brother was essentially normal. Aside from the cardiovascular differences, the contrasting personalities constituted the only striking difference noted in the twins. The healthy twin was always more robust physically and intellectually more alert than the hypertensive twin.

The hypertensive twin was by far the more dynamic of the two; he was more aggressive, more energetic, more conscientious and more active socially than his normal brother. The authors suggest that the element of rivalry, with constant repressed hostility, was the motivating factor of the latter's success; on the other hand, it may also have been responsible for his hypertension.

The evidence presented in this report suggests that renal ischemia is an incidental, and not a causative, factor in the pathogenesis of clinical hypertension. The similarity in the heredity and the early environment of the identical twins in this case stresses the divergence in personality drives as a possible cause of the hypertension present in one of them.

AUTHORS' ABSTRACT.

THE ANALYSIS OF A CASE OF COMPULSIVE MASTURBATION IN A CHILD. ELISABETH R. GELEERD, Psychoanalyt. Quart. **12**:520, 1943.

Geleerd shows that the compulsive masturbation in the young child whose case she reports had several determinants:

1. The child looked on her body as part of her mother's body. The mother's absence created a fear that her needs would not be satisfied, a fear which manifested itself through physical excitement; for this excitement masturbation was the physical outlet. It meant for the child that the mother was taking care of her.

2. The masturbation represented the little girl's fantasy of having a penis. She masturbated with this imaginary penis and showed it off in her exhibitionism.

3. All her fantasies—the positive and negative Oedipus fantasies, the fantasy of being beaten by the mother, the mother in the aggressive role of castrating her child, and the child's preoccupation with her genitals because she had no penis—found an outlet in her masturbation.

PEARSON, Philadelphia.

HYPNOSIS IN TREATMENT OF NEUROSIS DUE TO WAR AND TO OTHER CAUSES. CHARLES FISHER, War Med. **4**:565 (Dec.) 1943.

Fisher used hypnosis as a rapid form of therapy for traumatic neuroses. The therapeutic results were mostly in the nature of symptomatic cures, and none of the patients was cured in the sense that he had genuine insight into the unconscious mechanisms responsible for his symptoms. Hypnosis exerts a therapeutic effect in three ways: (1) by the use of direct suggestion; (2) by producing abreaction of repressed affect, and (3) by bringing into consciousness dissociated or repressed thoughts after the resistances have been broken through. The third way is indispensable for a genuine cure but is most difficult to carry out.

The results obtained through the use of hypnosis with pure suggestion and the bringing about of abreaction should not be minimized, particularly if a little interpretation of the unconscious material can be included.

PEARSON, Philadelphia.

MINNESOTA MULTIPHASIC PERSONALITY INVENTORY. CARLETON W. LEVERENZ, War Med. **4**:618 (Dec.) 1943.

In an experience of over one year the author found the Minnesota multiphasic personality inventory valuable in the neuropsychiatric service at the station hospital, Fort Snelling, Minn. It revealed hitherto unsuspected abnormalities in personality and assisted the clinician in arriving at an earlier and more accurate impression of the degree of abnormality. The clinical impression was not always corroborated by the scores obtained on the inventory, but the inventory made the examiner more aware of the existence of one or more abnormal changes in the personality which required evaluation.

PEARSON, Philadelphia.

ANXIETY NEUROSIS IN COMBATANTS. C. P. SYMONDS, Lancet **2**:785 (Dec. 25) 1943.

Symonds describes the anxiety neurosis as of two types: The first type can be explained by the theory of conflict. This assumes that the sense of anxiety arises from the conflict between fear of a given war situation and a sense of duty and loyalty. The second type is described as due to exaggeration of a normal fear response under extreme stimulation. Symonds believes the problem in cases of the second type is a question of the degree of affect, just as it is in many cases of severe depressive states. Such affect is generated in situations which do not cause similar fear in the so-called normal person. Thus, the occurrence of such a neurosis depends a great deal on the individual sensitivity to trauma of a psychic nature. Actually, the author believes, most war neuroses are of a mixed type, in which conflict and anxiety play part of the role and exaggerated fear the other part. The awareness of the condition may vary as much in a neurotic state as it does in any number of normal ranges of emotion. Therefore the degree of consciousness of one's conflict is not in itself a sign of how abnormal the conflict is, though it may influence the course and prognosis of the illness.

MCCARTER, Philadelphia.

Diseases of the Spinal Cord

PROTRUDED INTERVERTEBRAL DISK AND HYPERTROPHIED LIGAMENTUM FLAVUM: ANALYSES OF FIFTY SURGICALLY TREATED CASES. JOSEPH C. YASKIN and ANTHONY S. TORMAY, Am. J. M. Sc. **206**:227 (Aug.) 1943.

Yaskin and Tormay review 50 verified cases of protruded intervertebral disk. Thirty-one patients were males and 19 females, the average age being 39.6 years. In more than half the cases there was a history of trauma, which was slight as a rule. The average duration of symptoms was four and one-third years, and remissions were observed in 32 cases. The initial symptom was usually located in the back (middle and paravertebral portions). The pain was usually deep and was aggravated by bending, sneezing and coughing. In 42 cases the lesion caused major disability. The following abnormalities were encountered: diminished lordotic curve, 47 cases; tilting of the pelvis, 36 cases; muscular spasm, 48 cases; alteration of the knee jerk, 9 cases; alteration of the achilles reflex, 21 cases; hypesthesia, 4 cases, and a positive Lasègue sign, 42 cases. Tenderness of the sciatic nerve, often observed in cases of neuritis, was rarely seen. Myelographic study with air was a reliable diagnostic procedure. The operative results appeared gratifying in 36 of the 50 cases.

In differential diagnosis orthopedic, primary neurologic and visceral disease, systemic processes and psychalgias should be considered. In no case in which the diagnosis is reasonably certain should operation be regarded as desirable unless (1) previous adequate orthopedic and other treatment has been tried without improvement in the disability; (2) there is moderate to

major disability, and (3) attacks of major or of moderate disability for considerable periods frequently recur.

MICHAELS,
Medical Corps, Army of the United States.

THE PROBLEM OF HERNIATED NUCLEUS PULPOSUS IN THE MILITARY SERVICE. WILLIAM G. HAYNES, War Med. **3**:585 (June) 1943.

The symptoms of herniated nucleus pulposus consist of pain in the back or legs, along the distribution of the sciatic nerve, which follows a minimal amount of trauma and is made worse by coughing or sneezing. Examination reveals tenderness of the spinous process overlying the suspected disk, a positive Laségue sign and diminution in or absence of the achilles reflex.

Haynes reports on a series of 21 men with herniated nucleus pulposus. Eleven were discharged from the Army because of disability arising from a condition which existed prior to induction. Ten patients were operated on, and the protruded intervertebral disk was removed. None of these men returned to full duty. One was discharged with a diagnosis of psychoneurosis. Haynes attributes his high percentage of good results to a number of factors, which include: (1) careful selection of the patient for operation (he notes particularly that in the Army only men who are psychiatrically sound should be operated on for herniated nucleus pulposus); (2) use of the preoperative, operative and postoperative schedules and care which he describes, and (3) the fact that all the patients were strong, healthy young men.

PEARSON, Philadelphia.

Peripheral and Cranial Nerves

HEMATOPORPHYRINURIC NEURITIS. LEWIS A. GOLDEN, Am. J. M. Sc. **206**:474 (Oct.) 1943.

Up to 1940 less than 200 cases of hematoporphyrinuric neuritis had been reported in the literature. Golden reports the case of a white man aged 47, who was first seen in 1942 in a semiconscious, moderately delirious condition, occasionally groaning with pain and apparently dehydrated. Muscular weakness of the extensors of the wrists and feet was obvious. In 1940, after a laparotomy, transient paralysis of the left arm occurred, which lasted about five days. Intermittent colicky pains persisted until the patient's admission to the hospital. Bowel movements remained regular until two days after his admission, when diarrhea, with an average of ten to twenty stools a day, occurred. Urinary retention developed. On admission to the hospital, the blood pressure was 214 systolic and 110 diastolic, the pulse rate 120 and the temperature 99.4 F. The fundi showed moderate arteriosclerosis. Motor weakness of both upper and lower extremities was obvious, and wrist drop was apparent. On August 11 the urine was wine colored and showed a positive reaction for urobilinogen in a dilution of 1:258 and a positive reaction for uroporphyrin type 1. On August 12 the patient began to show bulbar symptoms, and the next day he died. The piaarachnoid was grayish white and showed scattered areas of thickening, 1 to 5 cm. in diameter. The anatomic diagnosis was cardiac hypertrophy, acute ulcerative colitis and chronic peritonitis. The leptomeninges were greatly thickened, and there was patchy loss of ganglion cells in the cortex. The clinical diagnosis was hematoporphyrinuria, of unknown cause. The disease appears to be a metabolic disturbance intimately connected with the synthesis and degradation of hemoglobin and is usually associated with the excessive excretion of porphyrin in the urine (porphyrinuria).

MICHAELS,
Medical Corps, Army of the United States.

PAIN IN THE SHOULDER GIRDLE, ARM AND PRECORDIUM DUE TO FORAMINAL COMPRESSION OF NERVE ROOTS. S. S. HANFLIG, Arch. Surg. **46**:652 (May) 1943.

Pain in the shoulder, arm or precordial region may be due to compression of a cervical nerve root. This type of pain is related to movements of the neck and is made worse by sudden increase of intraspinal pressure, but not by movements of the shoulder. Diagnostic aid is obtained by roentgenograms and by temporary application of overhead suspension traction.

The following conditions must be considered in the differential diagnosis: disorders of the shoulder joint, cervical rib syndrome, scalenus anticus syndrome, rupture of a cervical nucleus pulposus, tumor of the spinal cord, hypertrophic osteoarthritis of the cervical portion of the spine, cervical strain of postural origin, angina pectoris and psychoneurosis.

Overhead suspension traction relieves the pain due to narrowed intervertebral foramen with encroachment on a radicular nerve, such as occurs with arthritis of the cervical portion of the spine, but it is ineffective in cases of rupture of a cervical nucleus pulposus and of tumor of the cord; it increases the pain in cases of cervical rib and the scalenus anticus syndrome. In cases of psychoneurosis atypical responses are seen.

Head traction is a valuable therapeutic method; it may be applied as intermittent stretch by means of an overhead suspension device, with the patient in the sitting position, or as continuous traction by means of Sayre's sling, with the patient recumbent. The author prefers the former method because it is more rapid in its effect and does not require hospitalization.

LIST, Ann Arbor, Mich.

Treatment, Neurosurgery

TREATMENT OF ONE HUNDRED AND THIRTY-FOUR CASES OF MENINGOCOCCIC INFECTION WITH MASSIVE DOSES OF SULFADIAZINE. BRUNO A. MARANGONI and VINCENT C. D'AGATI, Am. J. M. Sc. **207**:67 (Jan.) 1944.

Marangoni and D'Agati analyze 134 consecutive cases of meningococcic infections encountered at a station hospital since March 13, 1942. The patients were all men, 10 of whom were Negroes. The ages varied from 18 to 44 years. Sulfadiazine therapy was employed, with the following basic plan of dosage: initial dose, 8 Gm.; second dose (two hours later), 5 Gm.; third and fourth doses (at four hour intervals), 4 Gm.; subsequent doses, 3 Gm. every four hours. The optimal sulfadiazine concentration in the blood was considered to be between 15 to 20 mg. per hundred cubic centimeters. In cases of fulminating meningococcic infection a 5 per cent solution of sodium sulfadiazine was given intravenously as the initial procedure.

The doses of sulfadiazine were much greater than those ordinarily employed. A mortality of 6.7 per cent (9 patients) was encountered for the entire group. Three patients exhibited meningococcemia with the Waterhouse-Friderichsen syndrome, and a fourth patient had meningococcic meningitis. Eight of 20 patients (40 per cent) treated with sulfanilamide had one or more toxic manifestations. A total of 28 per cent of the patients presented complications of various types

due to sulfadiazine, of which 86 per cent were renal in character.

The mortality rate of only 3.1 per cent for the treated patients and the absence of any fatalities or residuals which might be ascribed to the drug justified the use of massive doses of sulfadiazine.

MICHAELS,
Medical Corps, Army of the United States.

THE USE OF PHYTONCIDES IN THE TREATMENT OF INFECTED WOUNDS. I. V. TOROPTSEV and A. G. FILATOVA, Am. Rev. Soviet Med. **1**:244 (Feb.) 1944.

Toroptsev and Filatova report their observations on 11 patients who were given repeated phytoncide treatments. Seven of the patients had amputation of the arm; 1, of the thigh, and 3, of the foot. Eight of the wounds were purulent and contained streptococci, white staphylococci and other bacilli. In 2 patients amputation was complicated by gas gangrene, and in 1 patient, by frostbite. The flora of the wounds of the last 3 patients could not be determined. Osteomyelitis of the extremities was present in over 40 per cent of the patients. All the patients were anemic and had an elevated erythrocyte sedimentation rate. Prior to phytoncide treatment, all lesions showed evidence of inflammation, in some cases with a marked odor; edema of the soft tissues was also present.

The authors employed the following technic: Onions of high quality with bronze, dry peel were used. The part chosen was first examined for the activity of its phytoncides on protozoa. One third of the onion was freed from the dry leaves and ground quickly. The resulting paste was immediately placed in a Petri dish set 2 to 3 cm. from a previously prepared slide containing 1 drop of water with protozoa. The dish was covered. When the onion was sufficiently active, all the protozoa died in one to three minutes. Next, a glass vessel, with a diameter equal to that of the wound, was prepared. It has been the authors' experience that short chemical glasses are most suitable for wounds of the upper extremities and Koch dishes for stumps of the thighs.

Vaporization was performed daily as follows: The paste of one or two onions was placed in a previously prepared dish or glass and applied so that the surface of the wound did not come in direct contact with the paste. The stump was wrapped in several layers of cotton, so that the paste was protected from direct contact with the air. Vaporization was administered for ten minutes, usually in two intervals of five minutes each, at first with the paste of one onion and five minutes later with the fresh paste of another onion. After vaporization the wound was dressed. Before each treatment the wound was cleaned.

Toroptsev and Filatova state that after the initial phytoncide treatment, all wounds, without exception, become rose colored, instead of gray. A few patients had slight capillary hemorrhage; at the same time, they no longer complained of pain. After the second treatment purulence subsided, and the wound was no longer malodorous. The tissues of the injured extremities were bright red, but edema of the soft parts became more noticeable. In five days all wounds showed extensive epithelization. Edema of the soft parts rapidly disappeared, and many patients became free of pain.

The authors state that positive results were not obtained with all patients. Although the inflammatory process was arrested, there was a decided increase in granulation, with lack of epithelization in some parts of the wound. Such wounds contained ligatures and sequestrums, and the authors conclude that "phytoncides reduce the infection by freeing the potent or healthy elements of connective tissue."

GUTTMAN, Philadelphia.

ELECTRIC SHOCK THERAPY FOR PSYCHOSIS WITH SPECIAL REFERENCE TO DEMENTIA PARALYTICA. M. C. PETERSEN, Proc. Staff Meet., Mayo Clin. **19**:278 (May 31) 1944.

Petersen reports on the results of treatment of 458 patients with electrical shock. There were no deaths. Fifty-eight per cent of the patients with effective psychoses have adjusted socially, and the condition of 23 per cent has improved greatly. Of the patients with schizophrenia, 32 per cent of those with catatonia adjusted satisfactorily, as compared with 17 per cent of the patients with hebephrenia and paranoia.

Sixteen patients with dementia paralytica were treated with electrical shock. Improvement was noted in all these patients but was not pronounced in those with agitated and depressed states. The treatment was used only as an adjunct to fever therapy or to chemotherapy.

ALPERS, Philadelphia.

PENTOTHAL SODIUM ANESTHESIA IN NEUROLOGIC SURGERY. BARNES WOODHALL and ELIZABETH GOODMAN, War Med. **4**:556 (Dec.) 1943.

Woodhall and Goodman have used anesthesia induced with pentothal sodium, with air or combined with oxygen, in 378 varied neurosurgical procedures. With certain qualifications in respect to age and the degree of intracranial pressure, it has proved an ideal anesthetic agent for use in intracranial surgical procedures. Their experience with it in neurosurgical operations associated with shock suggests its potential value for major cranial wounds.

PEARSON, Philadelphia.

MANAGEMENT OF MENINGOCOCCIC INFECTIONS AT THE STATION HOSPITAL, FORT BENNING, GEORGIA. LOUIS OCHS JR. and MICHAEL PETERS, War Med. **4**:599 (Dec.) 1943.

The plan of treatment for meningococcic infections at the Station Hospital, Fort Benning, Ga., was as follows: Four grams of sulfadiazine was given orally as the initial dose, followed by 1 Gm. every four hours. A one-sixth molar solution of sodium lactate was given for the first forty-eight hours. The daily fluid intake was 3,000 to 4,000 cc. The urinary output was maintained at 1,500 cc. or over in twenty-four hours. All manifestations of drug toxicity and of shock were treated as soon as they arose. Serum or antitoxin was given when necessary, as were repeated lumbar punctures for the relief of intracranial pressure.

Seven patients so treated for seven days all recovered clinically and bacteriologically. All the patients had pain in the joints or in the tendons for six weeks after recovery.

PEARSON, Philadelphia.

IMPROVEMENT OF VISUAL AND OTHER FUNCTIONS BY COLD HIP BATHS. ARTHUR H. STEINHAUS and ALBERT KELSO, War Med. **4**:610 (Dec.) 1943.

A cold hip bath produces a striking temporary improvement in visual functions involving binocular vision, in visual acuity, in critical fusion frequency, in tapping rate and in eye to leg muscle reaction time. The improvement usually lasts two and one-half hours but may continue for at least six hours if no meal is eaten. There is no after-depression.

The studies indicate that a cold hip bath might be used in those aspects of warfare and industry that involve monotonous routine duties demanding acute vision and alert performance.

PEARSON, Philadelphia.

REACTIONS TO SULFONAMIDE COMPOUNDS. THOMAS F. FRIST, War Med. **5**:150 (March) 1944.

Frist reviews 186 cases of reactions to sulfonamide compounds. Among these are fever, cutaneous manifestations, hematuria, renal colic, azotemia, leukopenia, hepatitis, polyarthritis, conjunctivitis, cardiac complications, psychoses, peripheral neuritis, nausea and vomiting.

He describes cases in which there developed fever, agranulocytosis, renal damage, hemolytic anemia and interstitial myocarditis, and suggests the following simple rules, which, if carried out, will enable sulfonamide compounds to be used with relative safety:

1. The patient should be observed at least every other day for rash, conjunctivitis, jaundice, diarrhea, arthritis, drug fever and chills. 2. Urinalysis for the presence of red blood cells should be made every third day. 3. There should be adequate intake and output of fluid. 4. Sodium bicarbonate should be administered with each dose of the sulfonamide compound. 5. If the patient has had a previous toxic manifestation, he should be tested for reactions before being treated with the drug.

PEARSON, Philadelphia.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

CLARENCE A. NEYMANN, M.D., *President*

Regular Meeting, Jan. 6, 1944

NEUROPSYCHIATRY AT THE GREAT LAKES TRAINING STATION

General Aspects. LIEUT. COMDR. F. C. SOUTHWORTH (MC), U.S.N.R.; LIEUT. L. D. BOSHES (MC), U.S. N.R., and LIEUT. R. J. LEWINSKI, H(S), U.S.N.R.

A study of 14,000 men with neuropsychiatric coloring over a period of time revealed a constitutional psychopathic state, chiefly of the inadequate personality type, in 39.75 per cent, psychoneurosis in 25.12 per cent, mental deficiency in 12.75 per cent, enuresis in 6.20 per cent, a post-traumatic syndrome in 3.71 per cent, migraine in 2.77 per cent, somnambulism in 2.62 per cent, convulsive disorders in 2.51 per cent, illiteracy in 1.76 per cent, neurologic disorders in 1.40 per cent, alcoholism in 0.75 per cent, immaturity in 6.49 per cent and a history of psychosis in 0.17 per cent.

The importance of the Naval training stations in making decisions for retention or rejection of Navy personnel is emphasized. Primary screening of the recruit on arrival, with subsequent study in a specialized unit, if the case warrants further work-up, is discussed. The psychologic division of the unit is described. The work of the American Red Cross as the official social service agent of the Navy is praised. The use of trial duty for men with borderline conditions is emphasized, as are the duties of the various boards who eventually sit in session on neuropsychiatric cases. Standards of acceptance and their variations are considered and it is emphasized that more neuropsychiatrists are needed for the solution of current problems, as well as for treatment of Navy personnel who present discipline problems or who have returned from combat zones.

Special Aspects. COMDR. H. S. MILLETT (MC), U.S. N.R.; LIEUT. A. H. FECHNER (MC), U.S.N.R., and LIEUT. S. B. CUMMINGS, H(S), U.S.N.R.

The work of the Medical Survey Board in the study of men presenting problems of discipline who have had considerable service and of men who have been in combat is discussed. The number in either group is increasing gradually. The Board is aided in its final decision by personal observation of the members and by the information at hand, which includes the health record, the service record, the social service report and the brig psychiatrist's report. It is important to learn whether or not the present condition existed prior to entry into the service and whether military service has or has not aggravated the illness.

The two large groups of cases reviewed included cases of the constitutional psychopathic state, which made up 64.5 per cent of all cases reviewed by the Board. The subgroups comprised cases of emotional instability, 50 per cent; inadequate personality, 10.4 per cent, and schizoid personality, 41 per cent.

A small number of cases of the so-called war neuroses are reviewed; recommendations for discharge or retention were based on combat experience, number and severity of engagements, personal injury, personal fatigue and loss of sleep, anorexia and other symptoms. Almost two thirds of the returning men with war neuroses were recommended for shore duty—temporary or permanent—and the other one third was discharged from the Navy.

Neuropsychiatric and Psychologic Aspects of Discipline. LIEUT. J. L. KINNEY (MC), U.S.N.R.; LIEUT. COMDR. B. N. BENGTSON (MC), U.S.N.R., and LIEUT. L. A. PENNINGTON, H-V(S), U.S.N.R.

All prisoners admitted to the brig undergo a physical and medical examination, a psychologic study, a psychiatric interview and a "sociologic" study. Recommendations may include (1) action by the discipline officer, (2) study in the hospital along medical or psychiatric lines, (3) retention in the brig for further study by the staff and (4) referral of the prisoner to the neuropsychiatric unit for additional study.

Men admitted to the brig usually include those with "borderline" states who have been passed by draft boards, induction centers and psychiatric examiners; other persons admitted include those with emotionally immature, unstable or inadequate personalities.

Final dispositions may include (1) for men likely to adjust in the future, routine disciplinary action with restoration to duty; (2) for chronic repeaters, routine disciplinary action followed by discharge, in keeping with their records; (3) for men who are mentally ill but may be discharged into their own custody, a medical discharge, and, finally, (4) for the psychotic or the emotionally unstable patients, study in the hospital with final disposition.

DISCUSSION ON PRECEDING PAPERS

DR. GEORGE E. WAKERLIN, Chicago: As a physiologist, may I point out that constitutional psychopathic states and psychoneuroses unquestionably have physiologic and neurologic bases? Moreover, there is experimental evidence supporting this point of view. For instance, changes can be produced in various visceral organs by stimulation of certain portions of the cerebral cortex. There are of course connections between the cerebral cortex and the hypothalamus, which is the headwaters of the autonomic nervous system. Stimulation of the anterior hypothalamus in animals produces parasympathetic effects in various visceral structures, such as slowing of the heart, increased gastric secretion and increased gastrointestinal motility, and stimulation of the posterior hypothalamus gives sympathetic effects, such as an increase in heart rate, decrease in intestinal motility and increase in blood pressure. Lesions of the hypothalamus produced in the dog have given rise to gastric ulcer, which can be prevented by previous subdiaphragmatic vagotomy. Also, an appropriately placed lesion in the hypothalamus gives rise to the pseudoaffective state in animals. Prefrontal lobotomy, as is known, has been reported to reduce worrisome states in the human subject. These facts point to neurophysiologic bases for the psychoneuroses and the constitutional psychopathic states, as well as a neurogenic factor in peptic ulcer, mucous colitis, hypertension and other conditions.

Neurophysiologists and biochemists are making considerable progress in understanding the metabolism of the cells of the central nervous system, including those of the brain, as well as the mechanisms of synaptic transmission. The time will come when sufficient physiologic information will be available so that psychiatrists will understand what is happening in the brain and the nervous system of patients with psychoneuroses, constitutional psychopathic states and similar conditions.

Lieutenant Fechner and his associates mentioned that many psychiatric patients give family histories indicative of a hereditary factor. It should be remembered that any hereditary factor must operate through a physiologic mechanism. Thus, diabetes mellitus, although possessing a definite hereditary factor, usually operates through the physiologic mechanism of a decrease in the amount of insulin secreted by the islets of Langerhans. By the same token, constitutional psychopathic states and psychoneuroses must operate through certain physiologic and neurologic mechanisms.

In all three papers treatment was mentioned, and of course these men are in need of treatment. But more important than therapy is prophylaxis. As a citizen and a taxpayer, as well as a humanitarian, I am greatly interested in seeing these conditions prevented in the next generation, and I believe more can be done in this respect than is being done at present. After all, these conditions undoubtedly arise in part from the stimuli supplied by the environment. A more favorable control ought to be exercised over the environment of the children. Thus, a greatly expanded mental hygiene program is needed in this country, and psychiatrists should impress the general public more forcibly in regard to this need. I believe that if a better mental hygiene program existed within and outside the schools, many potentially unstable children would not grow up to have psychoneuroses and constitutional psychopathic states. I wonder, too, whether these conditions are not in part attendant on lack of proper sex education during adolescence and early adulthood. More should be done in this direction, particularly in the schools, although a good deal of education of the public in the matters of sex will be necessary before this is possible.

I should like to ask Lieutenant Commander Southworth whether he has any figures on the percentage of inductees rejected for neuropsychiatric reasons. Also, what percentage of the total number of rejectees does this constitute? I have seen various figures, published and unpublished, and they do not agree.

Dr. Francis J. Gerty, Chicago: I am informed that there is another person to be heard from; so I shall try not to take too much time. In private psychiatric practice, of course, the screening is about 100 per cent effective—all the patients referred have some nervous or mental trouble. The problem of the Navy is a different one. There seem to be two schools of thought on the matter: According to one school, the screening lets through too many persons who should have been eliminated; according to the other, too many persons have been screened out who should have been let through. I talked recently with a psychiatrist who is in charge of screening at another Naval training station. He expressed the belief that men were screened out who should have been let through. He seemed to have swung to a view the reverse of that presented here tonight. He expressed the opinion that the psychiatric examinations were tending to encourage a certain type of malingering, that is, simulation of neuropsychiatric conditions. Possibly there is merit in this view. Not long ago a man who was discharged from the Navy came to me to tell me that he had a terrible stigma. He had been assigned to one of the so-called suicide training units, having something to do with landing boats. He went to the chaplain during his period of training and said he was homosexual. Shortly thereafter he was discharged from the Navy. However, he did not like the type of notation on his discharge. When it became necessary to find a job, he did not like to tell employers why he had been discharged. He wanted to know what he could do to have this "mistake" rectified, as he actually was not homosexual. Of course there was nothing I could do about it. I note in Lieutenant Commander Southworth's paper that there is reference to the malingering of enuresis. I had not heard of that before. Possibly, neuropsychiatric information is spreading among the military forces and is being made use of in this manner. However, if a man malingers, it is questionable whether he will do very well in military service. I was interested to note that the truth of something which I think most psychiatrists had suspected has been demonstrated in Lieutenant Fechner's paper, namely, that some of the men with psychoneuroses seem to stand combat conditions well and that their difficulties center about things that most people are not in the habit of regarding as real, rather than about the real troubles. It is questionable as to how far we psychiatrists should go in the matter of returning to duty persons who we know have neuropsychiatric difficulties of one sort or another. It may be that the man will succeed under conditions of military service, even in combat areas, and he may seem at times to be good material for this purpose. That of course is not the long view of the matter. Every now and then I see men in the veterans hospital who got along fairly well under actual service conditions but who have been charging for it ever since. I do not say, however, that this constitutes the great bulk of patients who had service in the first world war. Many of them seem not to have contributed much to the military effort during the war but charge the same price afterward. I should be much interested to hear Dr. Hamill discuss the matter of enuresis.

Dr. Ralph Hamill, Chicago: Of course, with this wet crowd, the Navy, and with Davy Jones' locker right alongside, one could find all sorts of excuses for wetting the bed. Malingering seems rather serviceable, I should say. However, any one who takes advantage of it would not make a good companion on such a ship as I went out on two weeks ago. There were 300 men on it, and there was no room for any one who did not fit in and who did not want to do his part. Consequently, in my work on the induction board, I vacillate between the impression that a fellow is trying to fool me and the feeling that I don't care if he is trying to get out of service, I want to let him out; the vast majority of the men of his type are better out than in the Navy. After service, we taxpayers will pay for the care of men whose records state that their difficulty was increased in service.

Dr. L. W. Haus, Madison, Wis.: It has been my privilege to work on the induction board for the last three years, and, although I did not hear all of the first paper, I can say that my associates and I have seen all the conditions which Lieutenant Commander Southworth mentioned. I am surprised at the great number of men with neuropsychiatric conditions encountered at the naval station, for it is my policy and that of my associates to be as rigid as possible at the induction examination. I believe we do not discharge any man who should be in the service, but, in view of the great number of certified disability discharges which have resulted from the careless examinations of psychiatrists

who take the job as routine, we are inclined, like Dr. Hamill, to feel that a man who shows disinclination, together with emotional instability and other complaints, is better out of than in the service. For every candidate examined at the induction station, we can, in the allotted five or ten minutes, easily carry out the screening tests, which will relieve the reception station of any casualty which might develop. The war neuroses, however, are unpredictable. Even though the speaker stated that no direct relation exists between the intensity or length of exposure and the neurosis, I should like to ask him his opinion of the length of training which should precede the exposure to war service. It seems to me that all men should receive a thorough training before they are sent out to combat duty, a policy which, in my opinion, would reduce the incidence of war neuroses. Since the Navy is already inducting youths of 17, a preinduction training for boys of from 16 to 17 could be established and the final training given after the age of 18, an arrangement which would produce far better soldiers.

Dr. David Slight, Chicago: I have been astonished to hear of the large number of men discharged because of enuresis and somnambulism. In private and clinic practice one does not see many adults with such disorders, nor do I recall hearing that such a large percentage of men was discharged from the armed forces in World War I for these reasons. However, the percentage of men being rejected and discharged with all forms of neuropsychiatric disorders is greater in this war, and this may be a reflection of changes in medical standards and in the completeness of the examinations. Have any of the speakers had an opportunity to look up the statistics for men discharged with such disorders of personality maturity in World War I?

One cannot but note the high psychiatric standards adopted by the Navy. Likewise, the large percentage of cases classified under various subdivisions of the general heading "psychopathic personality" is noteworthy, as compared with the statistics for the Army.

Psychiatrists in the services should be watchful with regard to attaching psychiatric diagnoses to men who are proving inapt or troublesome. In many cases of such difficulty the standards of judgment and evaluation should perhaps not be psychiatric as one ordinarily understands the term. Thus, many men may be disgruntled, anxious to get out of the services, dissatisfied with their particular branch of the services, resentful of their immediate officers or assignments or upset by news from home. These factors may indeed be disturbing and interfere with the man's happiness, willingness or interest so that he appears inapt, if not troublesome, and is considered inefficient or undesirable for further service. I wonder, however, whether the psychiatrist should be the agent for the discharge of such men, or whether action for discharge should not properly be made through other channels and on grounds other than medical. In many such cases a discharge on medical grounds may have unfortunate reverberations later in claims for hospital care and pensions, as Dr. Hamill has suggested.

Lieut. Comdr. F. C. Southworth: In reply to Dr. Haus's question, most of these men had considerable experience in the Navy prior to combat. The average man in the Navy has recruit training; subsequently, he may or may not go to the service school, where he has additional training over a considerable period, and then prior to combat experience he has duty aboard ship. Most of the men have considerable experience before being sent into actual combat.

With regard to Dr. Haus's comment about the careful examination at the induction station at Great Lakes, a very small number of men come before our board from the Chicago Induction Station and from the northern stations in general. A large percentage of our men with severe disturbances come from other areas of the country, where the general level of education and social background is lower than here; so if we had only the Chicago and comparable stations, the need for our unit would almost cease to exist.

With regard to the comments of Dr. Gerty and Dr. Wakerlin concerning the number of rejectees and the question of whether too many or too few are screened out, it is the feeling of almost all the psychiatrists with whom I have talked and come in contact that few men are rejected who ought not to be. Although such men may, apparently, be able to carry on a normal life under civilian conditions, bitter experience in the last war has shown that many who broke down in the service became neurotic invalids for life. My associates and I attempt to some extent to eliminate men who we think will break down under battle conditions. We believe that few are rejected who ought not to be rejected. On the other hand, we are constantly under pressure to accept men who ought not to be accepted. The Man Power Commission, of course, is also under tremendous pressure. It has to provide men and has a hard time doing it. When we turn down a large number of men, the Commission doesn't like it; so we are always fighting to maintain our standards against that kind of pressure. At present we are probably keeping many men whom we ought not to keep, rather than rejecting many who should not be rejected.

As to the figures for the percentage of rejections, our data do not include the percentage of rejections at the induction stations, and I do not have that figure. Our own figures for rejections for neuropsychiatric reasons vary from time to time, according to the manpower situation, the number of men being inducted and the stage of the drafting process. For some time our figure was between 4 and 5 per cent of all recruits rejected for neuropsychiatric reasons alone. At certain times it crept up and approached 8 per cent. In recent months there has been a tightening of standards, apparently as a result of the Surgeon General's complaints that too many psychiatric casualties were developing in the war zones, and the general level has dropped again to between 4 and 5 per cent. That value, however, again is artificial because the number of rejections among Negroes is much higher. The proportion of rejections among Negroes varies anywhere from 8 to 10 per cent of the total number which we receive, so that if the Negro group were eliminated the level would drop probably to 4 per cent or a little less.

As Dr. Hamill indicated, the conditions of life on shipboard constitute an important factor, and one much more important in the Navy than in the Army because of the close contact into which the men are thrown. The problem of enuresis is a major one on a ship. The problem of homosexuality also becomes significant in a situation in which the contacts are so close and so long continued, and it is important to eliminate men with such a personality disorder.

I doubt whether enuresis and somnambulism are more common now than in the last war, but statistics are not accurate enough to prove the point. In the last war little effort was made to weed out men with such disorders, and a great many of them served in combat and, we believe, swelled the ranks of the invalids whom the government hospitalized for periods of years after the war. The diagnosis is made more frequently now because psychiatrists on the induction boards are trying to detect as many cases as possible. I doubt whether

there actually are more persons with these disturbances, but more men are being rejected for milder types of neurosis than was practiced in the last war. With respect to the point that the Navy seems to have more psychopaths than the Army has, it is true that there is a decided tendency, at least in our station, and I think in the Navy in general, to list as psychopathic, with emotional instability or with inadequate personality, a great many persons who in civilian practice would be called neurotic. Their symptoms are those of a neurosis, but they are called psychopaths because of the underlying condition which contributed to the development of the neurotic symptoms. They could quite well be called neurotic. The group of psychopathic states is heterogeneous and includes many conditions which would not ordinarily be considered in a discussion of psychopathic personalities as such. I think that the figure is rather high, even if it is not 40 per cent of the population. Just a word in conclusion about prophylaxis. Certainly, the treatment of these neuropsychiatric conditions has not been brilliant. In view of the great number of persons with such conditions in the population at large, and the fact that so many of them have not been seen by physicians or by clinics, psychiatrists should certainly lay more stress on the importance of the mental hygiene movement and make an effort to prevent these disorders in every possible way, particularly by more adequate training in the early years of life.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

CLARENCE P. OBERNDORF, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, Jan. 11, 1944

Neuro-Ophthalmologic Conditions: Moving Pictures. Presentation of Cases. DR. S. P. GOODHART and DR. B. H. BALSER.

CASE 1.—A 13 year old girl showed a congenital condition characterized by an abnormal movement of the right upper lid accompanying all forms of movement of the lower jaw, including voluntary movements (Marcus-Gunn phenomenon); in repose there was no apparent abnormality.

CASE 2.—From a boy aged 9 years a large cerebellar neoplasm was removed. Among the classic signs of the tumor was so-called skew deviation; on lateral gaze the homolateral eye turned downward and outward; the other eye synchronously turned upward and inward. This phenomenon is associated with lesions of the brain stem. Its presence here with a cerebellar process was doubtless due to secondary compression of the brain stem. With removal of the tumor the phenomenon disappeared.

CASES 3, 4 and 5.—Patients with multiple sclerosis showed various types of nystagmus.

CASE 6.—A patient with Weber's syndrome (alternating oculomotor hemiplegia) showed contralateral (right) hemiplegia with homolateral complete paralysis of the left third nerve; the vascular lesion was in the basis pedunculi at the level of the red nucleus on the left side.

CASE 7.—Unilateral Duane's syndrome is a congenital entity rarely encountered in which there is fibrosis of the levator palpebrae superioris muscle and of the external rectus muscle of one or of both eyes. This results in widening of the palpebral fissure as the eye turns laterally and in narrowing as it turns medially, as well as in limitation of lateral gaze in the affected eye.

CASE 8.—A patient with bilateral Duane's syndrome showed the characteristic phenomena, with involvement of both eyes.

CASE 9.—A patient with myasthenia gravis presented some of the ocular phenomena observed with this disease. The favorable influence of neostigmine was demonstrated.

CASE 10.—A patient with postepidemic encephalitis presented the unusual phenomenon of inability to open the voluntarily closed eyes; in order to do so the patient was obliged to carry out the associated movement of extreme hyperextension of the head.

CASE 11.—A patient with neuromyelitis optica presented evidence of involvement of the optic nerves, optic chiasm, optic tracts and spinal cord.

CASE 12.—A patient with extensive Recklinghausen's disease (neurofibromatosis) also presented, as a result of congenital absence of the posterior orbital wall, ptosis of the left eye and pulsating enophthalmos of the left eye, which was synchronous with the heart beat. On pressure over the left jugular vein in the neck, the eye bulged forward in a series of steps synchronous with the pulse. On coughing, the eye popped violently forward into an exophthalmic position, and the extraocular movements were limited to those of the internal rectus and superior oblique muscles. A roentgenogram showed absence of the greater wing of the sphenoid and a small portion of the lateral part of the lesser wing. Loss of movement of the left eyeball was due to absence of a bony wall for attachment of the extraocular muscles.

DISCUSSION

DR. H. A. RILEY: This presentation shows remarkably well the enormous material and interesting cases Dr. Goodhart has at the Montefiore Hospital. Much of it was so rapid that it was difficult for me to follow the pictures, and many features of the examinations were not sufficiently clear for me to understand entirely the various conditions presented.

The patient with unilateral nystagmus interested me. I did not think the condition was entirely unilateral. There seemed always to be some movement in the eye contralateral to the direction of gaze. This is not an uncommon condition; nystagmus predominant in the homolateral eye is frequently much more noticeable than in the eye contralateral to the direction of the gaze; this is especially true in patients with multiple sclerosis.

DR. S. P. GOODHART: Dr. Riley's suggestion that the pictures should be more slowly projected is in line with my own idea; I usually arrange for careful technical showing of the films so that I, myself, am not obliged to "chase the patients" as they are presented on the screen.

Postencephalitic Cyclothymia: Report of a Case. DR. FOSTER KENNEDY.

K. M., now aged 19, at the age of 9 years was referred to me by Dr. William St. Lawrence. She had fever, headache and a stiff neck; at the beginning of the illness there were prolonged light stupor, double vision and a count of 68 cells per cubic millimeter of spinal fluid. Dr. Tilney and I had no hesitation in making a diagnosis of encephalitis. The child was in bed five weeks. When the stupor had cleared, a peculiar condition became manifest. When she was sitting up

in bed, she would within half a minute be seen to have become largely immobilized. Her facial expression ceased to be animated; her eyes stared unwinkingly. She answered questions in a dull, monotonous voice, often making mistakes in her answers to simple questions about her age and address. During this phase, she was capable of adding 2 and 2 or 4 and 4, but made mistakes in adding 9 and 4 and 7 and 8, or added the figures quite irrationally, without any evidence of thought.

The limbs exhibited the waxy flexibility characteristic of certain catatonic states associated with "schizophrenia." The arms, if placed in a grotesque and uncomfortable position, remained unsupported, apparently without fatigue, until either they were replaced or she was ordered sharply to put them down.

At first these episodes occurred several times a day and lasted from five to forty minutes. They ended about as quickly as they began; that is, she would blink, rub her eyes, look animated, move about in bed and perhaps then slip out of bed and run about the room, with the childish gestures appropriate to her age. When she was asked what had been happening to her, she could never say more than that she "had felt queer and could not talk right."

After two months these episodes occurred only occasionally, when I ceased to see her; then she went to her home in the Middle West. About two years afterward I heard from friends that she was well but apparently very nervous. I was, therefore, not surprised when, in September 1941, I was again consulted because ever since her original illness she had been subject to a rhythm of fluctuating energy and emotion. This had settled into a constant pattern: a period of nine to thirteen days of elation, in which she looked very bright, was greatly animated and extremely restless, rarely sat down (and then only on the edge of her chair), had bursts of talk, did her lessons at top speed, and far more than was required, and slept little. On many occasions she was known not to have slept at all for six days and nights, this without any sign of fatigue but with loss of weight.

At the end of this period of elation she would within one day begin to slow up, grow quiet, become shut into herself, answer in monosyllables in a low, flat voice, work slowly at her lessons and have the general air of a middle-aged, faded nun. This state lasted from two to three weeks and was always followed by a period of elation, such as has been described.

Clearly, she had a manic-depressive psychosis, with a rapid swing in mood of curiously timed regularity. There was no history of emotional instability in her family. For years she had made engagements according to the way she knew she would be when the day came. They had not been able to keep her at boarding schools because in her elated periods she had kept all the girls in the dormitory awake by constant talking all night and every night, and had often insisted at 3 o'clock in the morning on saddling her horse and riding across country.

In 1941 I expressed the opinion that it might be possible to cure the episode with electrical treatment, but that the treatment had no prophylactic value for the future. I therefore did not think this therapy would be of benefit and did not administer the treatment until the spring of 1942. She has received only five treatments, each given at the beginning of a period of elation. They have always restored the normal rhythm of sleep and produced tranquility of emotion and behavior.

No treatment has been given, or required, since April 1943. She has been successfully maintained in boarding school, and her family report that she is better than she has ever been. In fact, since May 1943 the difference between her period of elation and her period of depression could be detected only by members of her family, who themselves said that perhaps they saw something unusual only because they were looking for it.

DISCUSSION

DR. GERALD R. JAMEISON: Dr. Kennedy's case is extremely interesting. However, I cannot see that this case of encephalitis, followed shortly by sharply defined, alternating periods of elation and depression, proves that there is an organic basis for cyclothymia. As a matter of fact, I do not believe that the clinical picture of the mood reaction is that of cyclothymia, at least not in terms of the adult reaction. It is quite evident that the patient had encephalitis, but it does not follow that because she has had a cyclic swing in mood since then her condition should be classified as manic-depressive psychosis. The disturbances of many children with encephalitis have been classified as schizophrenia, but I believe that most such conditions are organic, and not true schizophrenia, at least not in the clinical sense in which the disease is understood to exist in older people. However, there must be a physiologic factor in the usual cyclothymic reaction. In a single manic or a single depressive attack with complete recovery, it is easy to note that personality factors reacting to environmental stress have psychologic significance, needing evaluation and treatment. With the cyclothymic patients, however, irrespective of such factors, once the persistent swing in mood begins, psychologic treatment, or in fact any type of psychotherapy, is, unfortunately, limited in value. The inevitable course of the cycle continues. In such conditions it is easier to suspect that inherent elements of biologic nature influence the patient's personality. Some children are born with a tendency to be active, lively and aggressive, these manifestations being recognizable almost from the day the child is born. Other children are quiet, passive and subdued. How these tendencies are influenced by the environment probably has much to do with how the patient handles his emotional patterns. However, although Dr. Kennedy's patient had an organic condition producing a clinical picture which resembles a so-called functional psychosis, one cannot as yet believe that functional psychoses are actually of organic origin.

DR. RENATO ALMANSI: In connection with Dr. Kennedy's experience, it may be of interest to report a case of chronic encephalitis in a clinic patient who has been under observation for several months. The patient, a woman aged about 35, had encephalitis about twenty years ago and now shows postencephalitic parkinsonism. Since that time she has had oculogyric crises, with a rhythm of one, and sometimes two, attacks a week. They last from one to six hours and are accompanied by an obsessive attack, which begins with the onset of the crisis, lasts throughout and ends with it. If she is in the street, she feels that people are looking at her, and she runs home and shuts herself in. If she is in the house, she feels that people are looking through the window; so she pulls down the blinds. Even then she cannot rid herself of the idea that people are peeping under the blinds. This puts her in a severe state of anxiety, which lasts throughout the crisis. She has fairly good insight into the fact that there is no reason for this obsessive idea. I have seen mention of the same condition by von Economo (Encephalitis Lethargica, Berlin, Urban and Schwarzenberg, 1929, page 170), and Dr. Bernhard Dattner told me that he has seen a num-

ber of cases of obsession occurring during oculogyric crises.

DR. ISRAEL STRAUSS: Dr. Kennedy's case is of great interest because it opens an opportunity for speculation in a field in which psychiatrists are most ignorant. The patient unquestionably had encephalitis. The encephalitis progressed to a subacute stage. A pathologic process must have occurred in her brain which probably produced organic alterations. The changes may have been reversible, but it is known that in cases of the subacute form many of the lesions persist. There often follows a disturbance of function, which may produce a psychic disorder. After a period, that disturbance may again induce another change in physiologic function. The problem here, as I think Dr. Kennedy hints, is concerned with what has developed in the hypothalamus. It is possible that the lesion is there. It is known that psychic states can be produced by stimulation and other experimental means in that region of the brain. The hypothalamus is an area from which emotional excitement may be aroused. In the case under discussion the period of exaltation was followed rhythmically by a period of depression or a trancelike state. The problem is what can so alter the biologic activity of that part of the brain as to produce such wavelike swings of mood. Are they of chemical or of physical nature? How does electric treatment disturb the process to such an extent as to cause a return to the normal? Dr. Jameison believes that in these cases of recurrent manic-depressive psychosis a fundamental condition—he calls it the personality—must be present, and I should say there must be something inherently and fundamentally important in the biologic makeup of the individual patient. This something, of which one knows nothing, must facilitate the physiologic changes that produce these cyclic swings in mood. The importance of Dr. Kennedy's case lies in showing that search for conflicts in the unconscious or that the influence of environment will not of itself solve the problem of the innermost workings of the brain.

DR. RICHARD BRICKNER: It is worth while to recall the remarkable observations Foerster made while he was operating on a tumor of the third ventricle with the use of local anesthesia. When he touched various areas on the walls of the ventricle, the patient went into something resembling the manic state, which instantly ceased when the tactile stimulus was released. This reaction could be elicited or abolished at will. Foerster eventually reported 6 or 7 cases in which he obtained such responses.

DR. S. P. GOODHART: Dr. Kennedy has given an instructive and interesting discourse, with the presentation of an unusual case. I should hesitate, however, to call this case one of cyclothymia, as one understands the term. While there is often regularity, with rhythmic and predictable recurrences in adults, this does not seem to hold true in early life. What impresses me as striking and suggestive of a postencephalitic psychosis is just what is seen in the case of this girl; she showed not only episodes of somatic signs but regularity in the recurrence of psychic episodes, the basis being evidently an organic lesion, such as occurs with encephalitis. Recurrence and periodicity are characteristic of epidemic encephalitis. For example, I remember a patient at Montefiore Hospital with oculocephalogyric episodes which lasted exactly thirteen hours. Dr. Kennedy's case, likewise, raises the question of the relation of the psyche and the soma: I recall a patient who was admitted to Montefiore Hospital with all the distinctive features of postencephalitic parkinsonism; superimposed on the classic somatic signs were definitely psychogenic features. At my suggestion, one of my associates, Dr. Leo Stone, undertook hypnosis. After four or five interviews, during which hypnosis was induced, the patient emerged from his abnormal mental state, and the suppression of normal associated movements, rigidity, typical parkinsonism facies and excessive salivation had all disappeared. The transformation was striking. No further effort was made to hypnotize him. After a few weeks, however, he lapsed into his former parkinsonian state.

I wish to emphasize my own skepticism with regard to Dr. Kennedy's case. Though the alteration of mood is often predictable in adults, the swing of mood and behavior as presented by this child places the case on a pathophysiologic basis, such as is observed in epidemic encephalitis.

DR. C. P. OBERNDORF: The picture described by Dr. Kennedy is not one which is recognizable as that of cyclothymia. The patient had regular alternations of depression and elation every two weeks, which could be predicted. The ordinary concept of cyclothymia (and I presume by cyclothymia Dr. Kennedy means manic-depressive psychosis) is that of an unpredictable disorder, in which a person may not for many years have an attack either of elation or of depression. Dr. Kennedy's case has not been duplicated in my experience or in my reading. But I cannot quite follow his reasoning regarding the etiologic factors in cyclothymia. He mentioned the history of encephalitis in his case and he reasoned that a lesion affecting the hypothalamus in early childhood was responsible for the cyclothymia. In few cases is encephalitis in childhood followed by a manic-depressive psychosis. On the other hand, manic-depressive psychosis, or cyclothymia, occurs annually in thousands of people who have never exhibited any hint of an encephalitic disorder. I understood Dr. Kennedy to say that a lesion occurring in the hypothalamus at the time of the original illness was the basis for the disorder. Dr. Kennedy gave this child, now grown, electric shock therapy. Presumably it changed the lesion, or the residual malfunction of the hypothalamus, so that the young woman recovered. I should be interested to know just how Dr. Kennedy feels that this lesion in the hypothalamus was cured by electric treatment.

DR. FOSTER KENNEDY: This case is on the borderline of important things. It has to do with what I call the pathology of forces, which I believe will be the pathology of the future.

Dr. Oberndorf spoke of a lesion and asked me how electric treatment—which I did not call electric shock treatment—could change the lesion. We physicians have been so accustomed to consider that nothing exists if it cannot be seen under the microscope that by learning to see we have become blind.

I believe that Dr. Almansi, who described an obsessional state in association with an oculogyric crisis, had a case similar to mine. I have seen many supersaturated solutions of despair crystallize out an obsessional compulsion neurosis: a preoccupation with numbers; a preoccupation with cleanliness; a paranoid fear of ghosts, coming on in attacks, throughout life, associated with an underlying depression, the existence of the depression being often denied by the patient. Patients do not easily admit that they are mentally ill. They often translate their depression into a somatic symptom or into a compulsion neurosis. I think that the health, the stability, of the organism depends on the unstable equilibrium existing, as it does, between

opposed forces throughout nature. The nervous energy, the tonic energy, to use a familiar term, of the sympathetic nervous system is the accelerator, and the parasympathetic system acts as the brake. There is a good deal of evidence, some of which I cited in my paper entitled "The Hypothalamus: Pacemaker of the Organism" (J. A. M. A. **30**:2092 [May 25] 1940), that the hypothalamus maintains the balance between the energy of one system and that of the other. I do not know why in certain persons the balance becomes upset from time to time. It may become upset, as Dr. Jameison said, by precipitating circumstances, the influence of environmental distress. It also becomes disturbed for reasons of which one has no knowledge, and which produce such despair, if it is a depression, that the patient to integrate his own personality must find an explanation. And who cannot find some explanation in the circumstances of his life? A young woman says that she is in despair because she has been "a bad mother," in spite of the fact that her husband says she has been one of the best. A tailor in Newark says he is in despair because "his son is running his tailoring business to the dogs." Show him the books: It makes no matter. That is his stand, and he is going to fight it out on that line if it takes all summer! It helps him to have a reason for his terrible internal feeling, but one would be blind if one were to accept the patient's explanation of his trouble.

Dr. Goodhart stated that the manic-depressive psychosis is not regular in rhythm but that has not been entirely my experience. I can give Dr. Goodhart the case histories of at least a dozen persons I have seen in the last thirty years who have had a regular rhythm of depression and elation, many, oddly enough, a seasonal one. A physician's wife in this city is always elated for six months and depressed for six months. She has been like that for fifteen years. I have now a patient under my care who has been in that condition for the last eight years—five or six months one way and five or six months the other. I do not understand the reason, but I do know that one does not feel the rotation of the earth, one does not feel any of the things that are causing one to be alive and one is apt to think that forces of which one is unconscious have therefore no valid existence.

Platybasia: Report of a Case. Dr. B. C. Meyer (by invitation).

A woman aged 47 was first admitted to the Mount Sinai Hospital in May 1942, with the complaint that during the preceding year she had had attacks of burning pain in the back of the neck two or three times a day, accompanied by a sensation of difficulty in breathing and swallowing. For six months she had noted hoarseness, unsteadiness of gait, clumsiness and numbness of the upper limbs and impairment of memory. Examination revealed bilateral optic nerve atrophy, which was interpreted as primary. In addition, she displayed bilateral horizontal nystagmus, corneal analgesia and signs of involvement of the pyramidal pathways and of cerebellar function. Roentgenographic examination of the skull showed enlargement of the sella turcica with erosion of the dorsum sellae and the posterior clinoid processes. A tentative diagnosis of an intrasellar neoplasm was made, and roentgen ray therapy was instituted, without benefit. On readmission in September 1942, she displayed "onion peel" hypalgesia of the peripheral portion of the face, as well as hypalgesia and thermohypesthesia of the neck and body as low as the fourth dorsal dermatome. At this time the optic nerve atrophy was considered secondary. In addition to the signs referable to the pyramidal tract and the cerebellar dysfunction previously noted, there was impairment of deep sensibility in the upper extremities, especially on the right. Reexamination of the roentgenogram of the skull showed that the odontoid process extended above the so-called Chamberlain line. There was no construction or distortion of the foramen magnum. The protein content of the spinal fluid was 54 mg. per hundred cubic centimeters. The patient refused permission for ventriculographic study and was discharged. Eight months later she was readmitted because of severe exacerbation of symptoms. She had become bedridden and was unable to feed herself. Sensory disturbances now extended as far down as the tenth dorsal dermatome. The remainder of the examination revealed accentuation of the previous observations. Ventriculographic examination, performed by Dr. B. Schlesinger, showed symmetric hydrocephalus, with upward and forward displacement of the fourth ventricle. Dr. Ira Cohen performed a suboccipital craniotomy and cervical laminectomy, which revealed a large cyst lying within the cisterna magna and containing about 25 cc. of clear fluid. It extended upward between the cerebellar hemispheres, occupying the position of the vermis, and downward through the foramen magnum to the level of the atlas. The medulla oblongata was observed lying in the cervical canal as far down as the second cervical vertebra. A transverse ridge was noted opposite this vertebra, indicating that the latter had pressed against the zone of transition between the medulla and the cord. The neuraxis appeared somewhat softened at this point. The spinal nerves were noted to run cephalad to their foramens of exit. The cyst was emptied, and as much of its wall was removed as possible. After operation the patient showed remarkable improvement. She was able to walk and could care for herself. Examination before her final discharge revealed optic nerve atrophy, nystagmus, corneal analgesia, slight intention tremor and mild weakness of the legs. The other signs had disappeared.

The designation of the malformation in this case by the term platybasia is obviously an oversimplification. Disorders of the occipitoatlantal junction are rarely seen in pure form. Usually, there are encountered various combinations of anomalies, which may include platybasia or basilar impression, brevicollis (the Klippel-Feil deformity), the Arnold-Chiari malformation, malpositions of the axis in relation to the atlas and occiput and syringomyelia. The patient presented here revealed the association of the Arnold-Chiari deformity, a cyst of the cisterna magna and a mild degree of platybasia. Clearly, the last condition did not contribute directly to the production of the symptoms; yet the association of this mild deformity with other anomalies which did produce signs and symptoms indicates the importance of postulating such additional deformities in cases of platybasia in which the roentgenographic evidence is lacking.

DISCUSSION

Dr. Richard Brickner: Two clinical comments might be made: first, that attention was drawn to the search for the correct diagnosis by the relative shortness of the patient's neck; and, second, that in my experience the clinical picture shown by this woman is rare. The patient had a midline neurologic picture involving both the cervical portion of the cord and the medulla. Both sides of the face showed sensory involvement; the spinothalamic pathways from the arms and the upper part of the trunk were damaged on both sides, and there were also bilateral signs of injury to

the pyramidal tract; besides, there were bilateral cerebellar signs, presumably due to implication of the olivocerebellar tracts as they crossed. This was remarkable: Here was a lesion so situated that it seemed as if the interruption of pathways could have been made by a knife's cutting straight down, without any spread to the side; there was, for example, no evidence of involvement of structures even as slightly lateral as the hypoglossal nerves; one might have suspected some sign of impairment of this nerve, but the most careful search did not show it.

Another point worth mentioning is the "onion peel" type of trigeminal impairment. This condition is rarely seen, and, so far as I know, it has never been explained.

DR. H. A. RILEY: Cases of congenital changes in this vicinity are interesting. My colleagues and I had a patient at the institute with this condition, the so-called platybasia, or basilar invagination, with, as I remember the case, almost complete unilateral involvement of all the cranial nerves on the left side from the sixth down. This patient did not have any particular cerebellar signs; neither did he have any sensory lesions or signs referable to the pyramidal tract. He showed the same typical disturbance in the relation of the skull to the vertebral column as did Dr. Meyer's patient, only to a greater degree, and we accepted the diagnosis of platybasia. We were not able to explain satisfactorily why all the signs were unilateral, and after considerable study of the patient, with observation of increased protein in the spinal fluid, we were unwilling to rest on the diagnosis, because we thought the patient might have a flat area of meningioma on one side. The patient was operated on, but no meningioma was encountered. The patient is in the Goldwater Memorial Hospital with the same disturbance, namely, involvement of the cranial nerves on the left side from the sixth down, without any involvement of the cranial nerves on the right side or disturbance referable to the pyramidal tract. I think it is accepted that these disturbances of the cranial nerves are produced by tension and gradual degeneration of the cranial nerve particularly pulled on by the angulation of the stem.

In this presentation one feature should be mentioned particularly, the caudal migration of the medulla. The medulla actually does not migrate caudally in this condition or in the Arnold-Chiari deformity. What seems to happen is a premature fixation of the spinal cord caudally so that all the segments of the spinal cord and the medulla come to lie opposite portions of the segmented axis which are usually in relation to more caudal segments of the neuraxis. Under ordinary circumstances the spinal cord is drawn up within the vertebral canal until the conus lies opposite the disk between the first and the second lumbar vertebra. Under abnormal conditions the medulla and all the spinal segments are in relation to normally more caudally situated axial segments. The real situation is the interference with the normal ascent of the neuraxis within the vertebral column, so that it is not a caudal migration but a caudal displacement due to failure of ascent. In this case the enlargement of the foramen magnum was a definite indication that this condition was present. I did not see anteroposterior roentgenograms of the spinal axis, and I do not know whether any were taken. If such exposures had been made, it would probably have been seen that the upper part of the cervical canal was much larger than it should have been normally, in correspondence with the enlarged foramen magnum.

DR. BYRON STOOKEY: It is extremely difficult to accept Dr. Brickner's suggestion of a discrete lesion in the midline in this case. The scheme shows a split in the midline lying dorsal to the axis, and the roentgenograms show that the constructive process has extended into the foramen magnum. There are present therefore compression from the dorsal aspect by a cyst and compression from the ventral aspect; I do not see therefore how one can say this is a discrete lesion in the midline. It is entirely probable that the cyst compressed the dorsal columns and their nuclei and the rather large odontoid process extending forward compressed the ventral aspect of the axis, so that with compression of the spinal cord by two such space-occupying lesions within the foramen magnum it is questionable whether one should accept the diagnosis of a lesion "which can be drawn like a knife down the midline" and implicates the decussations of the trigeminal area. It seems to me that a definite mass occupies this entire area.

When I saw the roentgenogram, I thought the foramen magnum was enlarged. I should like to know whether Dr. Cohen and Dr. Meyer thought the foramen magnum was larger than normal, and whether it appeared to be so at operation.

DR. IRA COHEN: In answer to Dr. Stookey's question, the foramen magnum was enlarged rather than deformed, as it is supposed to be in basilar platybasia. In another case of basilar platybasia, I recall that the foramen was deformed, being triangular rather than enlarged.

DR. RICHARD BRICKNER: Dr. Stookey probably misunderstood me; if I used the word "lesion" I did not mean to do so. I was simply describing the clinical and anatomic picture the patient showed, regardless of the pathologic nature of the lesion.

DR. B. C. MEYER: In reply to Dr. Riley's question, I must explain that the artist who made the drawing erroneously introduced a few extra spinal nerves.

The roentgenologist did not interpret the foramen magnum as being pathologically enlarged.

I should like to add to what Dr. Stookey has said about Dr. Brickner's emphasis on involvement of some of the decussations in the medulla. First, I do not believe that one need postulate the presence of a lesion of the decussations in order to explain the "onion peel" type of hypalgesia of the peripheral aspects of the face. The latter can be accounted for by the involvement of the descending roots of the fifth nerve bilaterally. Second, in so far as the tumor was in the midline it affected structures in the midline. The fact, then, that the decussations were involved must be regarded as fortuitous, as was indicated by the prompt recovery of their functions after operation.

Meningocele Treated by Destruction of the Choroid Plexuses: Report of Cases. DR. TRACY J. PUTNAM.

In many cases of meningocele repair of the defect leads to development of hydrocephalus, and some of the most satisfactory cures from destruction of the choroid plexuses have been in such cases. In other cases plastic repair of the meningocele is rendered difficult or impossible because of the tension within the sac.

Three cases of meningocele are reported in which endoscopic cauterization of the choroid plexus was carried out as a primary operation. All the patients had been seen at other clinics; in 2 cases operation was considered impossible, and in the third it was attempted and abandoned. The third case was an unusual instance of interfrontal meningocele, which has shrunk to a nubbin of tissue after reduction of the intracranial pressure. In the other 2 cases the sac was in the lumbar region. In 1 of these cases the sac, which had been leaking

and become infected, healed to form a small button of tissue, obviously not in need of operation. The patient died several weeks later, of an intestinal disorder. In the other case the delicate, tense sac became small and tough, so that plastic repair could be carried out without difficulty. The functional result in the cases of the 2 surviving patients has been excellent.

DISCUSSION

DR. BYRON STOOKEY: Dr. Putnam has given an interesting method of reducing the size of the sac, which otherwise would be inoperable. I think the method can be used advantageously in cases in which an operation is really indicated and in which the promise of repair is good. I question the wisdom of the operation in certain cases. I have never forgotten an experience about twenty years ago; a mother came into the old Vanderbilt Clinic with a girl 7 or 8 years old who was paraplegic and incontinent and had trophic sores over the buttocks; the mother was frantic. No doubt the mother, when the child was an infant, had begged the surgeon to do the repair. The repair was done satisfactorily; the mesodermal structures were covered over, but the defect in the nervous system, obviously, could not be repaired, and the child, then 7 or 8 years old, was completely paralyzed. I have made it a practice never to operate on a patient with spina bifida who has paralysis of the legs, particularly if a girl, because when there is paralysis, especially of the muscles below the knee, control of the bladder is seldom regained. Perhaps it is a *tour de force* on the part of the surgeon to improve such a situation locally, but I wonder whether it is surgical wisdom. I do not mean to detract from the skill of the procedure; Dr. Putnam has presented a useful method, and his choice of material has not been in his favor. Certainly, this method would make easier repair in cases of meningocele in which it is worth while to do anything, and it has opened a way by which advancing hydrocephalus, which is a common complication of a successful repair, may be treated. The method takes care of the hydrocephalus which has in a number of instances complicated a successful repair in a patient who can walk and has prevented a favorable outcome. In such cases this method offers a great surgical advance. I still question whether I should have operated in this case or in the second case, in which there seemed to be paralysis of both legs. The toes seemed to be dorsiflexed, as though there was pronounced flaccidity of the flexor muscle. Although the mother is anxious to have this child now, I wonder whether she will be anxious to have it ten years from now. That is merely a matter of philosophy, and it does not detract from the value of the operation.

DR. H. A. RILEY: I should like to ask Dr. Putnam how much of the choroid plexus can be destroyed by the endoscopic method and whether the plexus in the temporal horn can be reached by this approach.

DR. C. P. OBERNDORF: The philosophic question which Dr. Stookey raised is one which always confronts the surgeon and physician in a case of such an apparently hopeless condition. Just now I am reading "The Little Locksmith," a remarkable autobiography of a woman who lay on her back from the age of 5 to 15 years. She has produced a book throwing much light on the thoughts of the physically handicapped, and one which I think will live for many years. One cannot foretell how the child's mind will develop, and as physicians we should attempt to see how we can benefit the patient, rather than take the matter of life and death into our own hands. Physicians often see only a "case" in an afflicted person—sometimes even in a child, for whom the parents feel deeply. The very fact that parents put all their love and attention into such an object—and it is an animate object—seems to make the philosophy of Dr. Putnam valid. I hope I have not anticipated what Dr. Putnam may be about to say.

DR. TRACY J. PUTNAM: To answer Dr. Riley's question first: It is usually possible to get all the choroid plexus down into the temporal lobe and into the foramen of Monro. The great bulk of the choroid plexus is in the glomus, in the body of the ventricle, and I am sure that something like 90 per cent of the secreting surface is in the glomus alone.

The point Dr. Stookey brought up is well taken. In the second case one leg was weak; the other was good, and there was good bladder control. When I recalled a patient on whom I operated ten years ago, who still has one weak leg in a brace but is a happy and intelligent child, I felt justified in operating in this second case. The third case was somewhat more problematic in that there was some weakness of both legs, but apparently sensation and bladder function were intact, and still are. The decision was more difficult; here, again, it looks as though this child were going to be the only one, and the parents were very anxious to have everything possible done; but perhaps I should not have acceded to their request. In my experience, it is difficult to know how much recovery of function will result from repair of a meningocele.

Aside from the question of function of the legs and sphincters, there is another criterion of operability in cases of meningocele, as well as in cases of hydrocephalus, which I think has received insufficient attention. I feel strongly that with either condition one should consider carefully the psychologist's estimate of the child's ability, and I feel much more opposed to operating on a baby who does not measure up to the performance expected from its age than I do in performing an operation where there is trouble with one leg. When there is weakness in both legs, the procedure becomes questionable indeed.

Defect in Synthesis of Acetylcholine in Patients with Myasthenia Gravis. DR. CLARA TORDO (by invitation) and DR. HAROLD G. WOLFF.

Since the discovery by Walker that patients with myasthenia gravis are helped by neostigmine, ideas concerning the nature of myasthenia gravis have been focused about three theories: (1) excessive destruction of acetylcholine due to unusually large amounts of choline esterase (demonstrated as unlikely by Milhorat), (2) defects in the ability of muscle to utilize acetylcholine (disproved by Lanari and Harvey and collaborators) and (3) decrease in the synthesis or release of acetylcholine.

The most plausible hypothesis is that there exists a defect in the synthesis of acetylcholine in patients with myasthenia gravis. Dr. Otto Loewi suggested that such synthesis be investigated. We are immeasurably indebted to Dr. Loewi for his enthusiastic interest in the development of the problem.

The synthesis of acetylcholine was studied according to a modified method of Quastel, Tennenbaum and Wheatley (*Biochem J.* **30**:1668, 1936). Uniform samples of nerve tissue, frog brain, for instance, under standard environmental conditions will synthesize acetylcholine at a fixed rate. The amount of acetylcholine synthesized was biologically assayed by measuring its effect in inducing contraction of the physostigminized rectus abdominis muscle of the frog. The relative ability of

two mediums to influence the synthesis of acetylcholine can thus be measured. In the study to be reported the effect on the synthesis of acetylcholine of serums from patients with myasthenia gravis was compared with the effect on the synthesis of acetylcholine of control serums.

Five healthy subjects and 57 patients with diseases other than myasthenia gravis served as controls. The amount of acetylcholine synthesized in the presence of the control serums during incubation for four hours at 37 C. averaged 2.08 micrograms per hundred milligrams of frog brain. The amount of acetylcholine synthesized in the presence of serum of control subjects deviated from the average not more than ± 15 per cent.

The amount of acetylcholine synthesized in the presence of serum of patients with myasthenia gravis was in all cases less than that synthesized by the control serum. The greatest defect was observed in the most seriously ill patient. The amount of acetylcholine synthesized in the presence of serum of patients seriously incapacitated with myasthenia gravis was less than half that synthesized by the control serum.

Spinal fluid exerted an effect similar to that of serum on the synthesis of acetylcholine. The effect of the spinal fluid of patients with myasthenia gravis on the synthesis of acetylcholine was compared with the effect of spinal fluid of patients with diseases other than myasthenia gravis. Here, also, a defect in the synthesis of acetylcholine was observed in patients with myasthenia gravis. The percentage of the defect in the presence of the spinal fluid of patients with myasthenia gravis was similar to the percentage of the defect in the presence of serum of the same patient.

Conclusion.—The decrease in synthesis of acetylcholine is apparently specific for myasthenia gravis, since it does not occur with other diseases presenting debility, cachexia, immobility and prostration. Also, the magnitude of the defect in the synthesis of acetylcholine is related to the severity of the myasthenia gravis. This depression of synthesis of acetylcholine in vitro suggests that there is a similar defect in the synthesis of acetylcholine in the body of patients with myasthenia gravis. It is probable that in patients with myasthenia gravis the acetylcholine available at the synapses eventually becomes insufficient for effective and repeated contraction of the muscle. This may manifest itself clinically in fatigability and muscular weakness. Neostigmine aids these patients by impeding the breakdown of the diminished quantities of acetylcholine.

Since the decreased synthesis of acetylcholine may be due to several factors, namely (1) lack of precursor substances, (2) lack of potentiator substances and (3) excess of inhibitor substances, several substances normally occurring in the body are being studied as to their effect on synthesis of acetylcholine in vitro.

DISCUSSION

DR. HERBERT C. STOERK: Because of the possible correlation between thymic tumor and myasthenia gravis, Mrs. Elvira Morpeth and I have studied the synthesis of acetylcholine in the rat brain according to the method of Quastel and associates in the presence of tissue from a thymoma which was obtained from a patient who died of myasthenia gravis and on whom autopsy was performed at the department of pathology of the College of Physicians and Surgeons. We then repeated the experiments of Torda and Wolff and studied the synthesis of acetylcholine, according to the method of Quastel and associates, in the presence of serum of patients with myasthenia gravis. We used rat brains instead of frog brains. We examined the serum of 6 patients whose condition had been diagnosed as myasthenia gravis at the Neurological Institute of New York, 2 of whom had severe symptoms. None of the samples examined showed any difference in the amount of acetylcholine formed after incubation, whether thymic tissue or serum from a patient with myasthenia gravis was added. I should like to ask Dr. Wolff and Dr. Torda whether they ever used brain tissue other than that of frogs.

DR. HAROLD G. WOLFF: That there is something wrong with the synthesis of acetylcholine in patients with myasthenia gravis must have occurred to investigators many times. I am sure that it has been put to test, I assume with negative results; otherwise, the defects in synthesis of this substance in patients with myasthenia gravis would have been called to the attention before this. The method which Dr. Torda has evolved has come through several phases, starting originally, as she mentioned, with the method of Quastel, Tennenbaum and Wheatley; she has modified this technic so that at present it looks as though one could demonstrate by means of her procedure a difference in the synthesis of acetylcholine in patients with myasthenia gravis. I call attention to the fact that this method is not as simple as it looks. If one takes the synthesis of control serum as 100 per cent, the serum of the patient so sick that she is barely able to breathe supports a synthesis of 40 per cent. That, after all, is not a great difference. Indeed, patients who have obvious but local myasthenia, with failure in ability to raise one eyelid, may have no demonstrable defect in synthesis. It is apparent, therefore, that we are working with a gross instrument, and that we are pointing out gross defects. I am sure that any subtlety in defect in synthesis is not shown. Although it may be assumed for the moment that the differences observed are valid (and these inferences will be challenged, and rightly so), difficulties still present themselves. Why is it that a defect so widespread as this seems to be if it can be demonstrated in the serum, would affect but a limited portion of the body? Why should the weakness be peculiar to the muscles about the eyes, perhaps for several years? If there is something in the blood stream which affects synthesis, why are not all muscles involved as are the ocular muscles? One is obliged to postulate that there is a difference in sensitivity in different nerve tissues. Dr. Torda has made assays for a few substances commonly found in the body to find out whether they are capable of modifying synthesis in the manner described. Extracts of the thyroid gland, salivary gland and lymph gland have no depressor effect. Extracts of thymus in very small amount interfere with synthesis. Pancreatic extracts also interfere with synthesis. Minced thymus in larger amounts accelerates the synthesis. Whether these observations have any bearing on the role of the thymus and pancreas in myasthenia gravis I am not prepared to say.

I should say, in closing, that we have a concept of the nature of myasthenia gravis. Persons with this disease are not capable of adequately supporting the synthesis of acetylcholine, an important substance in contraction of skeletal muscle.

DR. CLARA TORDA: We did not use rat brain for two reasons: (1) Under the circumstances of analysis, the percentage concentration of the enzyme which synthesizes acetylcholine is lower in the rat brain than in the frog brain, and (2) we used 100 mg. samples of a homogenized mixture of minced fresh brain of 28 frogs (100 mg. of tissue taken from one rat brain contains only a part of the brain). Therefore in our

experiments errors resulting from the difference of concentration of the enzyme in the different parts of the brain are probably eliminated. This procedure may also account for the relatively uniform results we obtained.

That results using serum of patients with myasthenia gravis differ from ours may be only an apparent contradiction. The fact that one is unable to demonstrate any difference in the amounts of acetylcholine synthesized in the presence of serum of control subjects as compared with that synthesized in Locke's solution indicates that the method is not sensitive enough to demonstrate slight differences in synthesis due to the presence or absence of substances in the serum of patients with myasthenia gravis. Possibly the use of rat brain introduces such a large amount of substrate as compared with the concentration of the enzyme that the requirements of the enzyme are completely fulfilled, so that the addition of more substrate in the form of serum is immaterial.

The statement that the addition of relatively large amounts of minced thymoma to the mixture did not modify the synthesis of acetylcholine may be due to the fact that presentations of thymoma contain large amounts of substances which potentiate the synthesis of acetylcholine, such as carbohydrates and amino acids, so that the effect of an inhibitor substance, if present, could be masked.

Book Reviews

Manual of Military Neuropsychiatry. Edited by Harry C. Solomon, M.D., Professor of Psychiatry, Harvard Medical School, and Paul I. Yakovlev, M.D., Clinical Director, Walter E. Fernald State School, Waltham, Mass., with the collaboration of other authorities. Price, $6. Pp. 764, with illustrations. Philadelphia: W. B. Saunders Company, 1944.

This is an excellent and timely addition to any neuropsychiatric library, even though it has been written primarily as a source of reference for the use of medical officers in the military services. It contains a great deal of practical material and up-to-date knowledge in connection with current neuropsychiatric problems in the armed forces, written by many of the most eminent authorities in the field of neuropsychiatry. Of the forty-six contributors, twenty are in active military service.

This manual represents an expansion of a series of lectures of the "Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including a Review Course in Military Neuropsychiatry," held at the Metropolitan State Hospital, Waltham, Mass., in 1941-1942. These lectures were privately published by the late Colonel Roy D. Halloran, superintendent of the hospital and director of the seminars. Because of the great demand for copies of the lectures from medical officers in the military services, Canada and overseas, and the limited supply, there resulted the present manual, which was planned to make them available to a large public. The manual is intended as a reference text on topics of clinical neurology and psychiatry and has been prepared especially for medical officers who, under the conditions of service in areas often remote from libraries, textbooks and other sources of readily accessible neuropsychiatric information, are deprived of these facilities. It should be noted, however, that the manual will be found useful by nonmilitary psychiatrists and others who are directly or indirectly interested in the psychiatric field.

The book is divided into an introductory chapter, written by Lieut. Col. Douglas A. Thom and Col. Roy D. Halloran, and five sections, entitled "Induction," "Administration and Disposition," "Clinical Entities," "Prophylaxis and Therapy" and "Special Topics." It is stressed that it has been difficult to assemble all the material on the prophylaxis and therapy of neuropsychiatric casualties, as a great deal of information pertaining to these specifically military aspects of neuropsychiatry is still restricted matter, and will remain so, probably until the termination of the war.

The manual contains a series of forty-nine articles. Section II considers such topics as neuropsychiatric screening at induction stations, military medical administration of induction stations, methods for rapidly securing a recorded personal history of inductees and psychiatric and neurologic examination of inductees. Section III discusses organization of the medical department and the duties of medical officer neuropsychiatrists; military laws and regulations pertaining to disposition of neuropsychiatric casualties; disposition of neuropsychiatric cases in the Army, the Air Forces, the Navy and the Merchant Marine at station hospitals and military camps, and military forensic neuropsychiatry.

Section IV, on the "Clinical Entities," has articles on "Psychoneurosis and Psychomatic Disorder," by Jacob B. Friesinger and Stanley Cobb; "Psychopathic Personalities," by William Malamud; "Alcohol and Alcoholism," by Edward A. Strecker; "Sexual Deviates," by Abraham Myerson; "Malingering," by Abraham Myerson; "Feebleminded and Defective Delinquents of Draft Age," by Ransom A. Greene and C. Stanley Raymond; "Epilepsy and Paroxysmal Neuropsychiatric Syndromes," by William G. Lennox; "Acute Psychotic Episodes and Acute Confusional Turmoil States in Soldiers," by Col. W. C. Porter; "Principal Psychoses," by Gaylord P. Coon, and "Common Diseases of the Nervous System and Syphilis of the Nervous System," by H. Houston Merritt. In other neurologic articles such topics are discussed as meningitis and encephalitis in the military services; peripheral nerve injuries and spinal cord injuries; craniocerebral injuries, and posttraumatic syndromes.

Section V includes chapters on "Psychology and Morale," "Mental Hygiene Clinics in Military Installations" and "Management of Neuropsychiatric Casualties in the Zone of Combat," by Lieut. Col. Roy B. Grinker and Major John P. Spiegel; "Emergency Care and Treatment of the Acute War Neurosis," by Lawrence S. Kubie; "Military Group Psychotherapy," "Rehabilitation of Military Offenders and Treatment of Alcoholic States," by Lieut. Col. Wilfred Bloomberg; "Shock Therapy in the Military Services," by Harry C. Solomon, and "Custodial Care and Management of Psychotic Soldiers and Occupational Therapy," by F. H. Sleeper.

In the section on special topics, or section VI, there are chapters on neuropsychiatric aspects and treatment of convoy and torpedo casualties, physiology of flying

and neuropsychiatric experiences of the foreign armies, as well as an article on electroencephalography, by Frederic A. Gibbs, which is especially well written and illustrated, with the addition of the latest bibliographic references on the subject. Most of the articles are sufficiently detailed to be considered good reference material, particularly since the latest bibliographic material is included.

The index, which contains sixty-seven double column pages, is especially valuable because of its fine detail, enabling one to obtain rapid and easy reference to the desired information.

Young Offenders: An Enquiry into Juvenile Delinquency. By A. M. Carr-Saunders, Hermann Mannheim and E. C. Rhodes. Pp. 168. New York: The MacMillan Company, 1944.

"Young Offenders," a volume of 168 pages, was written by A. M. Carr-Saunders, director of the London School of Economics, and Dr. E. C. Rhodes, reader in statistics and Dr. Hermann Mannheim, lecturer in criminology, both on the staff of the same school.

The authors worked under the auspices of the home office of the British government, which undertook an investigation of juvenile delinquency. The investigation began in October 1938 and covered the London area and six provincial cities.

The first of the book's four chapters deals with the history of previous investigations and cites many reports in part. The earlier reports were in general unsystematic and lacking in comparable standards, and the conclusions drawn were open to question. There was, however, a certain amount of uniformity of opinion, viz., concerning the predominant factors in juvenile delinquency.

These factors are: (*a*) the family factor—the broken home; (*b*) the environmental factor, in particular, educational mistakes or lack of education; unfavorable economic conditions, in particular, unsuitable or complete lack of employment, and the dangers inseparable from the growth of towns; (*c*) physical and mental defects, and (*d*) unsuitable methods of dealing with young offenders.

The earlier investigations, dating as far back as the post-Napoleonic period, were concerned primarily with the harm done by over-harsh penal methods and lack of education, and did not begin to take account of the psychologic factors. The present investigators, however, had hoped to make a parallel inquiry into the psychologic aspects; but, unfortunately, the war intervened, and their plans were not realized.

In the second chapter an attempt is made to disclose trends in juvenile delinquency, from a demonstration of statistical data collected during the present century. This examination was made with particular regard to (*a*) increasing juvenile crime; (*b*) geographic distribution; (*c*) age distribution, and (*d*) ratio of the frequency of adult crime to that of juvenile crime. Here, again, the authors encounter the difficulties inherent in analysis of statistical compilations not having comparable standards, with the added difficulty of frequent changes in legal position during the period covered.

The present investigation, covered in chapter 3, is restricted to recording of data relative to social and environmental conditions. The medical side was omitted. The investigation took six months, and the procedure consisted in recording information received from the probation office and the London City Council. Information was also recorded for nondelinquent youth (as a control) by the use of school data, an attempt being made to use a mate of the same age for each delinquent subject. Actually, the cases of 1,953 delinquent and 1,970 control children were investigated.

Special cards were designed for the recording of the data. These were obtained from replies to questions about the home, parents, siblings, cousins, aunts, uncles, etc., and environmental conditions and influences. These answers were recorded according to certain standards, for example, good, fair or bad. In the final chapter the authors summarize their conclusions and comment that the reader may be disappointed since their report does not adequately answer the question why juvenile delinquency has increased.

No single influence, characteristic or tendency could be described that would account for juvenile delinquency. Statistics are not enough. The problem cries out for psychologic understanding, and the authors are fully aware of this fact. Again and again the authors are compelled to express the hope that the psychiatrist can explain the inconsistencies which statistics reveal. They state: "There are boys, neither living under abnormal influences nor showing subnormal characteristics, so far as our data go, who become delinquent . . . and on the other hand, boys subject to abnormal influences and showing subnormal characteristics who do not become delinquent."

The book is difficult reading. Unless one has statistical yearnings, one is wafted away. On the other hand, if one can persevere, there is much to be gleaned. What the book fails to reveal challenges the psychiatrist.

Hypertension and Hypertensive Disease. By William Goldring and Herbert Chasis. Price, $3.50. Pp. 253, with 53 illustrations. New York: Commonwealth Fund, 1944.

The authors have written about a subject of which they have extensive clinical experience. They are to be commended for their knowledge and their application of physiologic processes and technics in the elucidation of the problem of hypertension. The book is not meant as an encyclopedic treatise on hypertension but represents a body of opinion based on facts obtained by the authors in their own experience. The point is stressed that hypertensive disease and the therapeutic methods used for overcoming it cannot be evaluated in terms of the level of the blood pressure alone. The use of this criterion is shown to be a common error. It is the authors' opinion that hypertension continues unchanged despite any effect on the level of the blood pressure, and that the latter is merely a secondary sign of, and not a causative factor in, hypertensive disease.

Their most fruitful section is the portion that deals with the specific hemodynamic changes and the renal functional and renal hemodynamic alterations associated with hypertension. Determinations of these factors are based on special physiologic methods in clinical medicine which the authors have used to good advantage. Their data indicate that in the great majority of patients hypertension does not result from a mechanism similar to that shown by Goldblatt in experiments with dogs. Few cases of hypertension caused by this mechanism have been encountered in their experience. They demonstrate that renal blood flow is normal in the early phases of hypertension and that it becomes impaired only much later in the course of the disease. Therefore, the renal disturbance is not primary but secondary.

There is a discussion of medical and surgical treatment. The authors indicate that psychotherapeutic management is one of the most important phases of the treatment of hypertension. Neuropsychiatrists, how-

ever, will miss observations on the effect of emotional factors in the genesis of this disorder. A critical evaluation by clinicians of the role of such factors would be of interest in the psychiatric field. An important observation which adds to the fund of facts in psychosomatic medicine is their observation on the effect of emotion on renal blood flow. During the investigative procedure on renal blood flow, 3 patients were frightened and experienced a serious state of alarm. The objective signs were pronounced sweating, pallor, restlessness and apprehension. During this period the renal blood flow decreased notably, and the filtration fraction increased, a condition indicating psychogenic vasoconstriction of the efferent glomerular arterioles.

The authors are frank to state that at present the etiologic factors in hypertension are unknown. They suspect a humoral mechanism with superimposed neurogenic factors.

This book is highly recommended.

One Hundred Years of American Psychiatry. Published by the Columbia University Press. New York: Columbia University Press, 1944. Price, $6. Pp. 650.

This volume was conceived several years ago, with the purpose of presenting a history of American psychiatry as a memorial for the centennial celebration of the American Psychiatric Association. The volume is intended to be a historical review of the evolutionary synthesis of a century of American psychiatry, and it stresses psychiatry as a growing cultural force. A chapter, entitled "Presenting this Volume," by Dr. Gregory Zilboorg, and a general historical survey, by Dr. G. K. Hall, serve as an introduction.

The book is composed of fourteen chapters, three of which deal with military psychiatry. Much time has been spent in research in the production of this book, and it is an excellent volume for historical reference. Included in the book are photographs of the original founders of the American Psychiatric Association and facsimiles of the signatures of the various presidents and the thirteen founding members. One of the defects of the work is the repetition of factual historical data. This is in part unavoidable, since each chapter is written by a different person.

Dr. Richard H. Shryock is the author of the chapter entitled "The Beginnings: From Colonial Days to the Foundation of the American Psychiatric Association." Dr. Henry E. Sigerist describes "Psychiatry in Europe at the Middle of the Nineteenth Century." An excellent chapter by Dr. Winfred Overholser covers the history of the founding and the founders of the association. Dr. Samuel Hamilton describes the history of the American hospitals for mental disease, and Dr. John C. Whitehorn reviews a century of psychiatric research in America. Dr. William Malamud contributes a survey of the history of psychiatric therapeutics, and Dr. Albert Deutsch reviews the history of mental hygiene. Military psychiatry is reviewed in terms of the advances made during the periods of the American Civil War, World War I and the present global war. In additional chapters the relation of psychology to psychiatry, the legal aspects of psychiatry and the influence of psychiatric thought on anthropology are reviewed.

A New German-English Psycho-Analytical Vocabulary. By Alix Strachey. Published by the Institute of Psycho-Analysis. Price, $2.50. Pp. 85. Baltimore: Williams and Wilkins Company, 1943.

This small volume, published by the Institute of Psycho-Analysis as one of the research supplements to the *International Journal of Psycho-Analysis,* is a timely and useful book. It aims to bring English translations of psychoanalytic literature up to date with modern German terminology and records the expansion and standardization of the vocabulary of psychoanalysis.

It is primarily designed to assist translators of psychoanalytic literature. The volume is an enlargement of what was formerly "The Glossary for the Use of Translators of Psychoanalytic Works."

It is recommended as a useful addition to the literature of every psychiatrist who is interested in reading psychoanalytic literature in the original German text.

News and Comment

THE SCIENTIFIC EXHIBIT, NINETY-FIFTH ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

Application blanks for space in the Scientific Exhibit at the Ninety-Fifth Annual Session of the American Medical Association, to be held at Philadelphia, June 18 to 22, 1945, are now available. Applications must be made on or before Feb. 12, 1945. The representative to the Scientific Exhibit from the Section on Nervous and Mental Diseases is Dr. F. P. Moersch, Mayo Clinic, Rochester, Minn.

Requests for application blanks may be addressed to Dr. Moersch or to the Director, the Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

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